PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 February 2001 (16.02.01)	
International application No. PCT/EP00/05783	**Applicant's or agent's file reference** 17394PC WAR
International filing date (day/month/year) 07 June 2000 (07.06.00)	**Priority date** (day/month/year) 07 June 1999 (07.06.99)
Applicant CALVET, Alain et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 December 2000 (15.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Olivia TEFY

Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US) PCT/EP00/05783

PATENT COOPERATION TREATY

9198095

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

POCHART, François
Cabinet Hirsch-Pochart
34, rue de Bassano
F-75008 Paris
FRANCE

Date of mailing (day/month/year)
03 January 2002 (03.01.02)

Applicant's or agent's file reference
17394PC WAR

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/05783

International filing date (day/month/year)
07 June 2000 (07.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
HAMON, Jacques
6, allée du Bellay
F-91400 Orsay
France

State of Nationality: FR
State of Residence: FR
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
HAMON, Jacques
39, route de la Touche
F-91530 Saint Maurice Montcouronne
France

State of Nationality: FR
State of Residence: FR
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Antonia MULLER
Telephone No.: (41-22) 338.83.38

09/926905

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

POCHART, François
Cabinet Hirsch-Pochart
34, rue de Bassano
F-75008 Paris
FRANCE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year) 03 January 2002 (03.01.02)	
Applicant's or agent's file reference 17394PC WAR	**IMPORTANT NOTIFICATION**
International application No. PCT/EP00/05783	**International filing date** (day/month/year) 07 June 2000 (07.06.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
HAMON, Jacques 6, allée du Bellay F-91400 Orsay France	FR	FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
HAMON, Jacques 39, route de la Touche F-91530 Saint Maurice Montcouronne France	FR	FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Antonia MULLER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
17394PC WAR		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 05783	07/06/2000	07/06/1999
Applicant		
WARNER-LAMBERT COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D221/20 A61K31/438 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 414 289 A (MERCK SHARP & DOHME) 27 February 1991 (1991-02-27) claims	1-13
Y	WO 94 17045 A (MERCK & CO INC ;HALE JEFFREY J (US); MACCOSS MALCOLM (US); MILLS S) 4 August 1994 (1994-08-04) claims	1-13
Y	US 5 439 914 A (CLAREMON DAVID A ET AL) 8 August 1995 (1995-08-08) claims	1-13
A	EP 0 431 943 A (MERCK & CO INC) 12 June 1991 (1991-06-12) claims	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2000	12/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 25604 A (SPRINGER MARTIN S ;MACCOSS MALCOLM (US); MERCK & CO INC (US); MILL) 18 June 1998 (1998-06-18) claims	1-13
P,A	US 6 013 644 A (SPRINGER MARTIN S ET AL) 11 January 2000 (2000-01-11) claims	1-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/05783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/05783

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
EP 0414289	A	27-02-1991	AT	101854	T	15-03-1994
			AU	628612	B	17-09-1992
			AU	5984490	A	31-01-1991
			CA	2021736	A	27-01-1991
			DE	69006799	D	31-03-1994
			DE	69006799	T	11-08-1994
			DK	414289	T	11-04-1994
			ES	2062303	T	16-12-1994
			JP	3184959	A	12-08-1991
			NO	903315	A	28-01-1991
			NZ	234557	A	23-12-1992
			PT	94806	A	20-03-1991
			ZA	9005841	A	26-06-1991
WO 9417045	A	04-08-1994	AT	169001	T	15-08-1998
			AU	693087	B	25-06-1998
			AU	6126894	A	15-08-1994
			CA	2154569	A	04-08-1994
			DE	69412067	D	03-09-1998
			DE	69412067	T	25-03-1999
			DK	681571	T	23-11-1998
			EP	0681571	A	15-11-1995
			ES	2119174	T	01-10-1998
			JP	8505880	T	25-06-1996
			US	5869496	A	09-02-1999
US 5439914	A	08-08-1995	AU	1920895	A	04-09-1995
			CA	2182733	A	24-08-1995
			EP	0745086	A	04-12-1996
			JP	9509177	T	16-09-1997
			WO	9522548	A	24-08-1995
EP 0431943	A	12-06-1991	AT	168377	T	15-08-1998
			AU	6329794	A	21-07-1994
			AU	6787390	A	13-06-1991
			CA	2031633	A	09-06-1991
			CN	1053613	A	07-08-1991
			CN	1110685	A	25-10-1995
			DE	69032480	D	20-08-1998
			DE	69032480	T	06-05-1999
			ES	2118715	T	01-10-1998
			FI	906045	A	09-06-1991
			JP	2016496	C	19-02-1996
			JP	4217960	A	07-08-1992
			JP	7047576	B	24-05-1995
			NO	905306	A	10-06-1991
			NZ	236315	A	27-09-1994
			PT	96126	A	30-09-1991
			US	5633247	A	27-05-1997
			US	5206240	A	27-04-1993
			ZA	9009836	A	25-09-1991
WO 9825604	A	18-06-1998	AU	5604998	A	03-07-1998
			US	6013664	A	11-01-2000
US 6013644	A	11-01-2000	NONE			

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 17394PC WAR

Express Mail No. EF378134286US

Box No. I TITLE OF INVENTION

TRICYCLIC ANALGESICS

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WARNER-LAMBERT COMPANY
201 Tabor Road
MORRIS PLAINS, NJ 07950
USA

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

CALVET Alain
3475 Creekside Drive
Ann Arbor, MI 48105
USA

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

POCHART François
CABINET HIRSCH-POCHART
34, rue de Bassano
75008 PARIS
FRANCE

Telephone No. 01.53.23.92.12

Facsimile No. 01.47.23.49.13

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

JACOBELLI Henri
65, avenue du Général de Gaulle
91550 PARAY-VIEILLE-POSTE
FRANCE

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PUAUD Jocelyne
29, chemin de la mère Dieu
91310 MONTLHERY
FRANCE

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

ROMAN François J.
11, allée Pierre Fresnay
94400 VITRY-SUR-SEINE
FRANCE

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HAMON Jacques
6, allée Du Bellay
91400 ORSAY
FRANCE

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Sheet No. 3 . . . .

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GROUHEL Agnès
2, rue des Peupliers
92190 MEUDON LA FORET
FRANCE

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

- [x] **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- [x] **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- [x] **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- [x] **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- [x] **AE** United Arab Emirates
- [x] **AL** Albania
- [ ] **AM** Armenia
- [ ] **AT** Austria
- [x] **AU** Australia
- [ ] **AZ** Azerbaijan
- [x] **BA** Bosnia and Herzegovina
- [x] **BB** Barbados
- [x] **BG** Bulgaria
- [x] **BR** Brazil
- [ ] **BY** Belarus
- [x] **CA** Canada
- [ ] **CH and LI** Switzerland and Liechtenstein
- [x] **CN** China
- [x] **CR** Costa Rica
- [x] **CU** Cuba
- [x] **CZ** Czech Republic
- [ ] **DE** Germany
- [ ] **DK** Denmark
- [x] **DM** Dominica
- [x] **EE** Estonia
- [ ] **ES** Spain
- [ ] **FI** Finland
- [ ] **GB** United Kingdom
- [x] **GD** Grenada
- [x] **GE** Georgia
- [ ] **GH** Ghana
- [ ] **GM** Gambia
- [x] **HR** Croatia
- [x] **HU** Hungary
- [x] **ID** Indonesia
- [x] **IL** Israel
- [x] **IN** India
- [x] **IS** Iceland
- [x] **JP** Japan
- [ ] **KE** Kenya
- [ ] **KG** Kyrgyzstan
- [x] **KP** Democratic People's Republic of Korea
- [x] **KR** Republic of Korea
- [ ] **KZ** Kazakhstan
- [x] **LC** Saint Lucia
- [x] **LK** Sri Lanka
- [x] **LR** Liberia
- [ ] **LS** Lesotho
- [x] **LT** Lithuania
- [ ] **LU** Luxembourg
- [x] **LV** Latvia
- [x] **MA** Morocco
- [ ] **MD** Republic of Moldova
- [x] **MG** Madagascar
- [x] **MK** The former Yugoslav Republic of Macedonia
- [x] **MN** Mongolia
- [ ] **MW** Malawi
- [x] **MX** Mexico
- [x] **NO** Norway
- [x] **NZ** New Zealand
- [x] **PL** Poland
- [ ] **PT** Portugal
- [x] **RO** Romania
- [ ] **RU** Russian Federation
- [ ] **SD** Sudan
- [ ] **SE** Sweden
- [x] **SG** Singapore
- [x] **SI** Slovenia
- [x] **SK** Slovakia
- [x] **SL** Sierra Leone
- [ ] **TJ** Tajikistan
- [ ] **TM** Turkmenistan
- [x] **TR** Turkey
- [x] **TT** Trinidad and Tobago
- [ ] **TZ** United Republic of Tanzania
- [x] **UA** Ukraine
- [ ] **UG** Uganda
- [x] **US** United States of America
- [x] **UZ** Uzbekistan
- [x] **VN** Viet Nam
- [x] **YU** Yugoslavia
- [x] **ZA** South Africa
- [ ] **ZW** Zimbabwe

Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

- [x] DZ Algeria
- [x] AG Antigua & Barbuda

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;

(vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Box IV - OTHER AGENTS

ROCHET Michel
CORTEY Pierre
Cabinet HIRSCH-POCHART
34, rue de Bassano
75008 PARIS
FRANCE

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) June 07, 1999	US 60/137,868	US		
item (2)				
item (3)				

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s):

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* : ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 6
description (excluding sequence listing part)	48
claims	10
abstract	: 1
drawings	:
sequence listing part of description	:
Total number of sheets	65

This international application is **accompanied** by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

POCHART François

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference 17394PC WAR 163

Applicant
WARNER-LAMBERT COMPANY

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 102,00 EUR [T]

2. SEARCH FEE . . . . . 945,00 EUR [S]

International search to be carried out by _____

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 65 sheets.

first 30 sheets . . . . . 409,00 EUR [b1]

35 (remaining sheets) x 9,00 EUR (additional amount) = 315,00 EUR [b2]

Add amounts entered at b1 and b2 and enter total at B . . . . 724,00 EUR [B]

Designation Fees

The international application contains 57 designations.

8 (number of designation fees payable *(maximum 8)*) x 88,00 EUR (amount of designation fee) = 704,00 EUR [D]

Add amounts entered at B and D and enter total at I . . . . . 1428,00 EUR [I]

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . [P]

5. TOTAL FEES PAYABLE . . . . . 2475,00 EUR

Add amounts entered at T, S, I and P, and enter total in the TOTAL box — TOTAL

[ ] The designation fees are not paid at this time.

MODE OF PAYMENT

[x] authorization to charge deposit account (see below)	[ ] bank draft	[ ] coupons
[ ] cheque	[ ] cash	[ ] other *(specify):*
[ ] postal money order	[ ] revenue stamps	

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ EP

[x] is hereby authorized to charge the total fees indicated above to my deposit account.

[x] *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

[x] is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

2 804 0070	June 07, 2000	POCHART François
Deposit Account No.	Date *(day/month/year)*	Signature

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) *(Names should be indicated as they appear in the request)*:

WARNER-LAMBERT COMPANY, 201 Tabor Road, MORRIS PLAINS, NJ 07950 - USA

hereby appoints (appoint) the following person as: ☒ agent ☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

POCHART François, CORTEY Pierre, ROCHET Michel
CABINET HIRSCH-DESROUSSEAUX-POCHART
34 rue de Bassano
75008 PARIS
FRANCE

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: TRICYCLIC ANALGESICS

Applicant's or agent's file reference: 17394PC WAR

International application number (if already available):

filed with the following Office OEB as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)*:

Date: April 17, 2000

Rose Armstrong, Assistant Secretary

Form PCT/Model of power of attorney (for a given international application) (July 1992)

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) *(Names should be indicated as they appear in the request)*:

CALVET Alain, 3475 Creekside Drive, ANN ARBOR MI 48105 USA

hereby appoints (appoint) the following person as: ☒ agent ☐ common representative

Name and address

(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

POCHART François, CORTEY Pierre, ROCHET Michel
CABINET HIRSCH-DESROUSSEAUX-POCHART
34 rue de Bassano
75008 PARIS
FRANCE

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: TRICYCLIC ANALGESICS

Applicant's or agent's file reference: 17394PC WAR

International application number (if already available):

filed with the following Office OEB as receiving Office
and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)*:

Date: April 17th 2003 Alain Calvet

Form PCT/Model of power of attorney (for a given international application) (July 1992)

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) *(Names should be indicated as they appear in the request)*:

GROUHEL Agnes, 2 rue des Peupliers, 92190 MEUDON - FRANCE
HAMON Jacques, 6 Allée du Bellay, 91400 ORSAY - FRANCE
JACOBELLI Henri, 65 Avenue du Général de Gaulle, 91550 PARAY VIEILLE POSTE - FRANCE
PUAUD Jocelyne, 29 Chemin de la Mère Dieu, 91310 MONTLHERY - FRANCE
ROMAN François Joseph, 11 Allée Pierre-Fresnay, 94400 VITRY-SUR-SEINE - FRANCE

hereby appoints (appoint) the following person as: ☒ agent ☐ common representative

Name and address
(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

POCHART François, CORTEY Pierre, ROCHET Michel
CABINET HIRSCH-DESROUSSEAUX-POCHART
34 rue de Bassano
75008 PARIS
FRANCE

to represent the undersigned before

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: TRICYCLIC ANALGESICS

Applicant's or agent's file reference: 17394PC WAR

International application number (if already available):

filed with the following Office OEB as receiving Office
and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) *(where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power)*:

A. Grouhel J. Hamon H. Jacobelli

J. Puaud F-J. Roman

Date: 22 Mars 2000

Form PCT/Model of power of attorney (for a given international application) (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
17394PC WAR		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05783	07/06/2000	07/06/1999
International Patent Classification (IPC) or national classification and IPC		
C07D221/00		
Applicant		
WARNER-LAMBERT COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/12/2000	29.08.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Cortés, J. Telephone No. +49 89 2399 8206

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05783

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-48 as originally filed

Claims, No.:

1-13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 10-13.

because:

☒ the said international application, or the said claims Nos. 10-13 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2, 4, 6-8, 10-13
	No:	Claims	1, 3, 5, 9
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-9

No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 10-13 relate to subject matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents cited in the search report are referred to in this communication:

D1: EP-A-0 414 289 (MERCK SHARP & DOHME) 27 February 1991 (1991-02-27)

D2: WO 94 17045 A (MERCK & CO INC; HALE JEFFREY J (US); MACCOSS MALCOLM (US); MILLS S) 4 August 1994 (1994-08-04)

D3: US-A-5 439 914 (CLAREMON DAVID A ET AL) 8 August 1995 (1995-08-08)

D4: EP-A-0 431 943 (MERCK & CO INC) 12 June 1991 (1991-06-12)

D5: WO 98 25604 A (SPRINGER MARTIN S; MACCOSS MALCOLM (US); MERCK & CO INC (US); MILL) 18 June 1998 (1998-06-18)

Novelty

Present compounds are encompassed by the generic formula in D5 (D5: e.g. claim 1, column 52), and the starting compound in example 78, namely spiro(6-methoxyindan-1-one[2.4]piperidine is within the scope of present claims 1, 3, 5 (D5: e.g. page 85 and spiro(indane-1-one[2.4]piperidine) derivatives in claims 3 and 9, columns 57 and 62).

Therefore, present claims 1, 3, 5 and 9 are not novel in view of D5 (Article 33(3) PCT).

Present compounds differ from the ones in D1 in the spiro(cycloalkaphenyl[2.4]piperidine) structure. The compounds of D1 have a spiro(cycloalkaphenyl[1.4]piperidine) structure (D1: e.g. claim 1, page 25).

Present compounds are encompassed by the generic formula in D2 (D2: e.g. claim 1, page 69), but differ from close related sub-groups or specific compounds in D2 in the above mentioned structural feature (D2: e.g. claims 11 and 12, pages 95-101).

Present compounds differ from the compounds in D3 in that both R^1 and R^2 can be hydrogen, or, provided that one of both is not hydrogen, in that this substituent is then in 1-position of the cycloalkaphenyl and not in 4-position (D3: e.g. claim 1, column 29).

Present compounds are encompassed by the generic formula in D4 (D4: e.g. claim 1, page 155), but differ from close related sub-groups or specific compounds in D4 in the spiro(cycloalkaphenyl[2.4]piperidine) structure (D4: e.g. claims 2-3, 7-8, pages 159, 161-162). The closest related compounds in D4 have a spiro(cycloalkaphenyl[2.3]piperidine) structure (D4: e.g. examples 501-502, page 149).

Present compounds are a novel specific selection of the compounds generically disclosed in D2 and D4.

Inventive Step

D2 discloses structurally related compounds for the same medical use and can be regarded as the closest prior art.

Since present compounds are encompassed by the generic formula in D2, it was obvious they would have analgesic properties.

The problem of the invention must therefore be formulated as the provision of new analgesics with unexpected properties or advantages when compared to the closest related compounds known from D2.

In the absence of any such evidence, present application does not comply with the requirements of inventiveness according to Article 33(3) PCT.

Industrial Applicability

For the assesment of the present claims 10-13 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can be dependent upon the formulation of the claims. The EPO, for instance, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but may allow claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Reference is made to the following P-document:

D6: US-A-6 013 644 (SPRINGER MARTIN S ET AL) 11 January 2000 (2000-01-11)

The priority documents pertaining to the present application were not examined at the time of establishing this report. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the P-documents ... cited in the international search report could become relevant to asses whether the present claims satisfy the criteria set forth in Article 33(1) PCT.

Re Item VII
Certain defects in the international application

The description does not mention the closest prior art represented by the above cited documents as required by Rule 5.1(a)(ii) and (iii) PCT.

Re Item VIII
Certain observations on the international application

Many compounds of claims 6-8 are listed several times (e.g. 2. compound in claim 6; conciseness, Article 6 PCT).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

09/980,965

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 December 2000 (14.12.2000)

PCT

(10) International Publication Number
WO 00/075116 A3

(51) International Patent Classification[7]: C07D 221/20, A61K 31/438, A61P 25/00

(21) International Application Number: PCT/EP00/05783

(22) International Filing Date: 7 June 2000 (07.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/137,868 7 June 1999 (07.06.1999) US

(71) Applicant *(for all designated States except US)*: WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CALVET, Alain [FR/US]; 3475 Creekside Drive, Ann Arbor, MI 48105 (US). JACOBELLI, Henri [FR/FR]; 65, avenue du Général de Gaulle, F-91550 Paray-Vieille-Poste (FR). PUAUD, Jocelyne [FR/FR]; 29, chemin de la mère Dieu, F-91310 Montlhery (FR). ROMAN, François, J. [FR/FR]; 11, allée Pierre Fresnay, F-94400 Vitry-sur-Seine (FR). HAMON, Jacques [FR/FR]; 39, route de la Touche, F-91530 Saint Maurice Montcouronne (FR). GROUHEL, Agnès [FR/FR]; 2, rue des Peupliers, F-92190 Meudon la Foret (FR).

(74) Agents: POCHART, François et al.; Cabinet Hirsch-Pochart, 34, rue de Bassano, F-75008 Paris (FR).

(81) Designated States *(national)*: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

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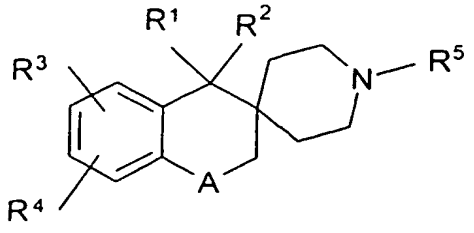
4 July 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TRICYCLIC ANALGESICS



(I)

(57) Abstract: A tricyclic compound of Formula (I): wherein: R^1 is hydrogen or hydroxy; R^2 is hydrogen or hydroxy; or R^1 and R^2 together are oxygen; A is a bond, CH_2, CH CH_3, CH_2 CH_2 or $C(CH_3)_2$; R^3 and R^4 are the same or different and are hydrogen, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, trifluoromethyl, NO_2, COR^6, $COOR^6$ or NR^6R^7, wherein R^6 and R^7 are the same or different and are hydrogen, C_1-C_6 alkyl or benzyl; R^5 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, (O=C)-C_{1-6} alkyl, (O=C)-C_{2-6} alkenyl, (O=C)-C_{3-6} cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl groups can be substituted by 1, 2 or 3 groups selected from halo, C_3-C_6 cycloalkyl, phenyl or substituted phenyl, and salts thereof, are particularly useful for treating, among other indications, neuropathic pain and other CNS disorders.

WO 00/075116 A3

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/EP 00/05783

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D221/20 A61K31/438 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 414 289 A (MERCK SHARP & DOHME) 27 February 1991 (1991-02-27) claims	1-13
Y	WO 94 17045 A (MERCK & CO INC ;HALE JEFFREY J (US); MACCOSS MALCOLM (US); MILLS S) 4 August 1994 (1994-08-04) claims	1-13
Y	US 5 439 914 A (CLAREMON DAVID A ET AL) 8 August 1995 (1995-08-08) claims	1-13
A	EP 0 431 943 A (MERCK & CO INC) 12 June 1991 (1991-06-12) claims	1-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2000	12/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 00/05783

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 25604 A (SPRINGER MARTIN S ;MACCOSS MALCOLM (US); MERCK & CO INC (US); MILL) 18 June 1998 (1998-06-18) claims	1-13
P,A	US 6 013 644 A (SPRINGER MARTIN S ET AL) 11 January 2000 (2000-01-11) claims	1-13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Ir. ıational application No.
PCT/EP 00/05783

Box I Observations where c rtain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 10-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members . . .

Inter ...onal Application No
PCT/EP 00/05783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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09/980965
JC13 Rec'd PCT/PTO 04 DEC 2001
PCT/EP00/05783

TRICYCLIC ANALGESICS

FIELD OF THE INVENTION

The invention relates to organic compounds characterized as having a fused bicyclic ring system substituted with a spiro nitrogen-containing third ring. The compounds are effective for treating seizures and chronic pain in mammals.

BACKGROUND OF THE INVENTION

Although chronic pain is a frequent condition in the population, its pathophysiology is not well understood. One possibility is that nociceptive spinal sensory neurons generate inappropriate activity after injury. Spinal sensory neurons become hyperexcitable and generate spontaneous impulses after injury in experimental animals, and in humans. Matzner and Devor (1992) proposed that the hyperexcitability associated with chronic pain results from an increase of Na channel density at the site of injury. It has also been hypothesized that, after nerve injury, changes in the kinetics and voltage-dependent characteristics of Na currents contribute to the ectopic impulse generation and hyperexcitability of spinal sensory neurons. Dorsal root ganglion (DRG) neurons possess a complex mix of Na currents, including a fast tetrodotoxin-sensitive (TTX-S) current and a slow TTX-resistant (TTX-R) current. In rat DRG neurons, PGE_2, adenosine and serotonin, three agents that produce hyperalgesia in vivo, increase the magnitude of the TTX-R current, and shift its conductance/voltage relationship in a hyperpolarized direction (Gold *et al.*, 1996). Following nerve injury, TTX-R currents are down regulated in DRG neurons, and, in the same animals, TTX-S currents are upregulated (Cummings and Waxman, 1997). Using a Na channel specific antibody, Devor *et al.* (1993) evidenced an accumulation of Na channels in the neuroma resulting from a nerve section; the accumulation of Na channels at injured axonal tips may explain the ectopic channel excitability and the resulting

pain and paresthesia which frequently complicate peripheral nerve injury in humans.

Injury to the axons of spinal sensory neurons appear to modify Na currents, substantially altering their excitability; Thus, selective blockers of Na channels can be used for the prevention or treatment of chronic pain in mammals. Sodium channel blockers have been shown effective in chronic pain syndromes, including trigeminal neuralgia, diabetic neuropathy, migraine prophylaxia and cancer pain (review by McQuay *et al.* ,1995, British Medical Journal, 1995; 311: 1047-1052, and references cited therein).

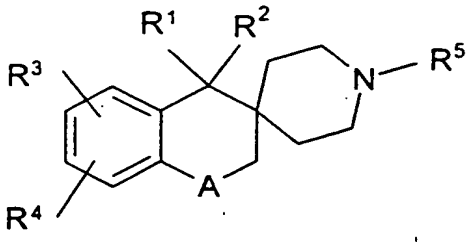
However, pain due to acute or chronic nerve injury is difficult to treat, and is often resistant to conventional analgesics. Such compounds include some local anesthetics and anticonvulsants, for example lidocaine, etidocaine, benzocaine, tetracain, riluzole, phenytoin, and gabapentin. Most of them, even though such agents modulate Na channels, have limited clinical use because of high risks of adverse events. Lidocaine, for example, can cause cardiovascular collapse and resultant cardiac arrest. Benzocaine, can cause respiratory distress, as well as skin rash, erythema and oedema. The use of phenytoin for seizure disorders can result in hyperglycemia.

Because there is no effective chemical treatment for neuropathic pain, e.g. chronic pain, and since such pain is typically associated with diseases such as cancer, as well as severe physical injuries and diabetic neuropathy, the need continues to find compounds which can be utilized clinically without resulting in severe adverse events.

SUMMARY OF THE INVENTION

The inventors have now discovered a series of tricyclic compounds which are potent antagonists of neuronal Na channels. The compounds are characterized as fused bicyclic ring systems having a spiro third ring substitution.

The invention therefore provides tricyclic compounds of Formula I:



(I)

wherein:

R^1 is hydrogen or hydroxy;

R^2 is hydrogen or hydroxy; or

R^1 and R^2 together are oxygen ;

A is a bond, CH_2, CH CH_3, CH_2 CH_2 or $C(CH_3)_2$;

R^3 and R^4 are the same or different and are hydrogen, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, trifluoromethyl, NO_2, COR^6, $COOR^6$ or NR^6R^7, wherein R^6 and R^7 are the same or different and are hydrogen, C_1-C_6 alkyl or benzyl ;

R^5 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl, (O=C)-C_{1-6} alkyl, (O=C)- C_{2-6} alkenyl, (O=C)-C_{3-6} cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl groups can be substituted by 1, 2 or 3 groups selected from halo, C_3-C_6 cycloalkyl, phenyl or substituted phenyl,

and the pharmacentically acceptable salts thereof.

The compounds of the invention are useful in the clinical management and treatment of various conditions such as seizure disorders, epilepsy, neuroprotection, preferably for conditions such as cerebral ischemia, hypoxia and head trauma, local anesthesia, pain, preferably acute, chronic, neuropathic, visceral and somatic pain, irritable bowel syndrom (IBS), the treatment of drug dependence, migraine and obsessional compulsive disorders.

Preferred compounds are those of Formula I wherein R^5 is hydrogen, C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group.

Other preferred compounds are those of Formula I wherein R^5 is C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group.

Other preferred compounds are those of Formula I wherein R^5 is hydrogen, C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group and R^3 is hydrogen or C_1-C_4 alkoxy.

Most preferred compounds of the invention are compounds of Formula I wherein R^1 and R^2 together are oxygen and A is CH_2.

Other most preferred compounds are those of formula I wherein R^5 is H, C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group and R^3 is hydrogen or C_1-C_4 alkoxy.

Another embodiment of this invention is a pharmaceutical formulation comprising a compound of Formula I admixed with a pharmaceutically acceptable carrier or diluent.

A further embodiment of the present invention is a method for treating a mammal suffering from pain and in need of treatment, comprising administering an effective amount of a compound of Formula I.

Still another embodiment of the invention is a method for treating a seizure disorder in a mammal in need of treatment, comprising administering a compound of Formula I.

Methods of treatment of all the further indications referred to above also fall within the scope of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "C_1-C_6 alkyl" means a straight or branched carbon chain made up of from one to six carbon atoms. Examples of C_1-C_6 alkyl groups include methyl, ethyl, isopropyl, *sec*-butyl, *tert*-butyl, isopentyl and *n*-hexyl.

"C_1-C_6 alkoxy" means the foregoing alkyl groups bonded through oxygen, for example methoxy, isopropoxy, and *n*-hexyloxy.

"C_2-C_6 alkenyl" means a straight or branched carbon chain having from two to six carbon atoms, with one carbon-carbon double bond present in the chain. Examples include ethenyl, 2-propenyl, 1-methyl-3-pentenyl, 1-ethyl-2-butenyl, and 5-hexenyl.

"C_3-C_6 cycloalkyl" means a non-aromatic cyclic ring having from three to six carbon atoms, examples being cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The foregoing alkyl, alkenyl and cycloalkyl groups may be substituted by 1, 2 or 3 groups selected from halo, unsubstituted C_3-C_6 cycloalkyl, phenyl or substituted phenyl. "Halo" means chloro, bromo, fluoro and iodo. "Substituted phenyl" means a phenyl group having 1, 2 or 3 substituents selected from halo, hydroxy, nitro, unsubstituted C_1-C_6 alkyl, unsubstituted C_1-C_6 alkoxy, and NH_2.

Examples of C_1-C_6 alkyl groups substituted with cycloalkyl thus include cyclopropylmethyl, 1-cyclobutylethyl, 3-cyclohexylbutyl and 3,3-dicyclohexylpropyl. Alkyl groups substituted with halo include chloromethyl, 1,2-dibromoethyl, trifluoromethyl, and 1-bromo-3-chloro-6-iodohexyl. Alkyl groups substituted with phenyl or with substituted phenyl include benzyl, 1-phenylpropyl, 1-methyl-3-phenyl-butyl, 3-chlorophenylmethyl, 2,3-dimethoxybenzyl, 3-(2-methyl-5-fluoro-6-nitrophenyl)-butyl, and 3,3-diphenylpropyl.

Examples of substituted C_2-C_6 alkenyl groups include 2-cyclobutylethenyl, 3-phenyl-2-butenyl, 1,1-dimethyl-3-chloro-3-butenyl, 4,4-diphenyl-3-butenyl, 2-

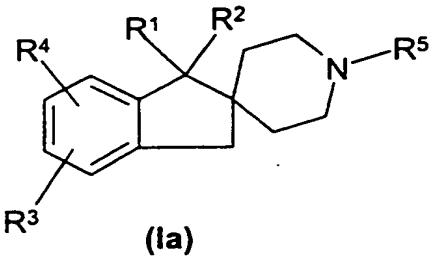
(3-chlorophenyl)-3-cylclobutyl-4-hexenyl, and 1,2-difluoro-3-(2-phenyl-cyclobutyl)-4-pentenyl.

Examples of substituted C_3-C_6 cycloalkyl groups include 3-cyclopentylcyclohexyl, 2-phenylcyclobutyl, 3-chlorocyclopentyl, 2,2-dibromo-3-nitrocyclohexyl, and 2,2-di-(3-methoxyphenyl)-cyclopropyl.

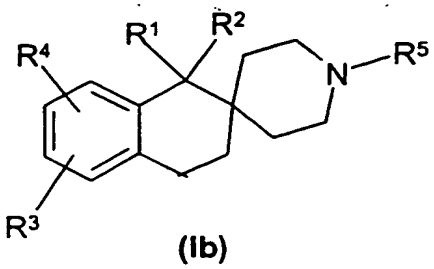
Examples of substituted C_1-C_6 alkoxy groups include trichloromethoxy, cyclopropylmethoxy, 1-methyl-2-phenylpropoxy and 2,3-di-(2,4-dinitrophenyl)-hexyloxy.

The alkyl, alkenyl and cycloalkyl substituent groups can be bonded through a carbonyl (O=C) group. Examples include acetyl, pivaloyl, 1-oxo-3-pentenyl, 1-oxocyclobutylmethyl, 1-oxo-3-phenyl-4-cyclohexylpentyl, and 1-oxo-(3-phenylcyclopentyl)-methyl.

"-A-" in Formula I is defined as a bond, $-CH_2-$, $-CH-CH_3$, $-CH-(CH_3)_2$ and $-CH_2CH_2-$; the invention compounds can thus have the following general structures:



(Ia)



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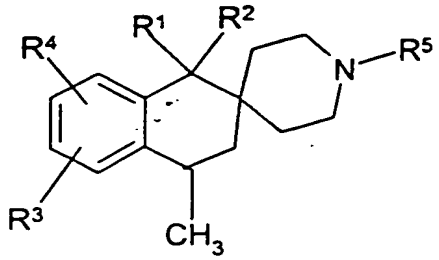
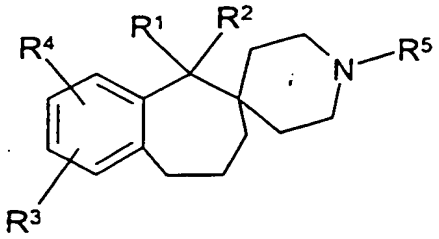


(Ic)



(Id)

Preferred compounds of the present invention include the following:

3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

3,4-dihydro -1'-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'- allyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(2-methylpropyl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropionyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) - 1' (trans-2-phenyl-methylcyclopropyl) ;

3,4-dihydro -1'-benzyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(di-p-fluorobenzhydryl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine];

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihyd· ·· -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-mc oxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclobutylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclohexylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(2-phenylethyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

More preferred compounds of the invention include the following:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine];

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) -3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl -3,4-dihydro-4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl -3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

Most preferred compounds of the invention include the following:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

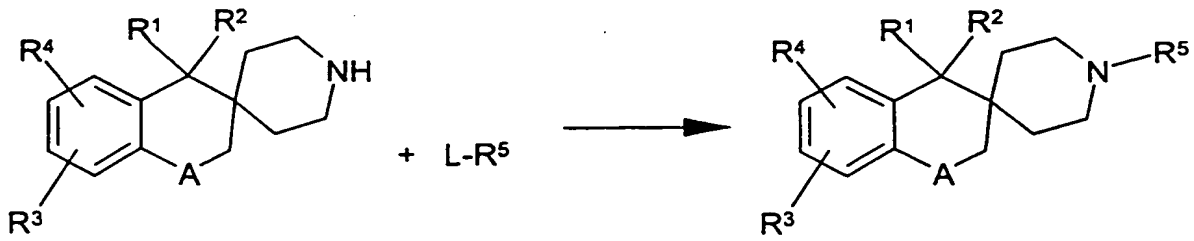
3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

The compounds of Formula I are characterized by being bicyclic rings having a spiro ring as a substituent group. The spiro ring contains a nitrogen atom (i.e. N-R^5), which can be basic in nature when R^5 is a group such as alkyl, alkenyl or cycloalkyl. Such basic compounds readily form pharmaceutically acceptable salts by reaction with common inorganic and organic acids. Typical acids utilized to form the pharmaceutically acceptable salts of the invention include hydro-

chloric, sulfuric, sulfamic , phosphoric , citric , succinic , glutamic , maleic , lactic, tartaric, *p*-toluenesulfonic, benzoic , oxalic and salicyclic acid. The salts are prepared by simply contacting the spiro base with the appropriate acid, generally in a solvent such as methanol or diethyl ether. The salts generally are highly crystalline, readily precipitate, and are recovered by filtration. They can be further purified if desired by recrystallization from common solvents such as methanol, ethyl acetate, acetone and tetrahydrofuran.

The invention compounds of Formula I are readily prepared by methodologies well known in the art of organic chemistry. It is preferred to simply first prepare a compound wherein R^5 is hydrogen, and then react this compound with R^5-alkylating or -acylating agents. Such reaction is shown in scheme 1 below :

Scheme 1



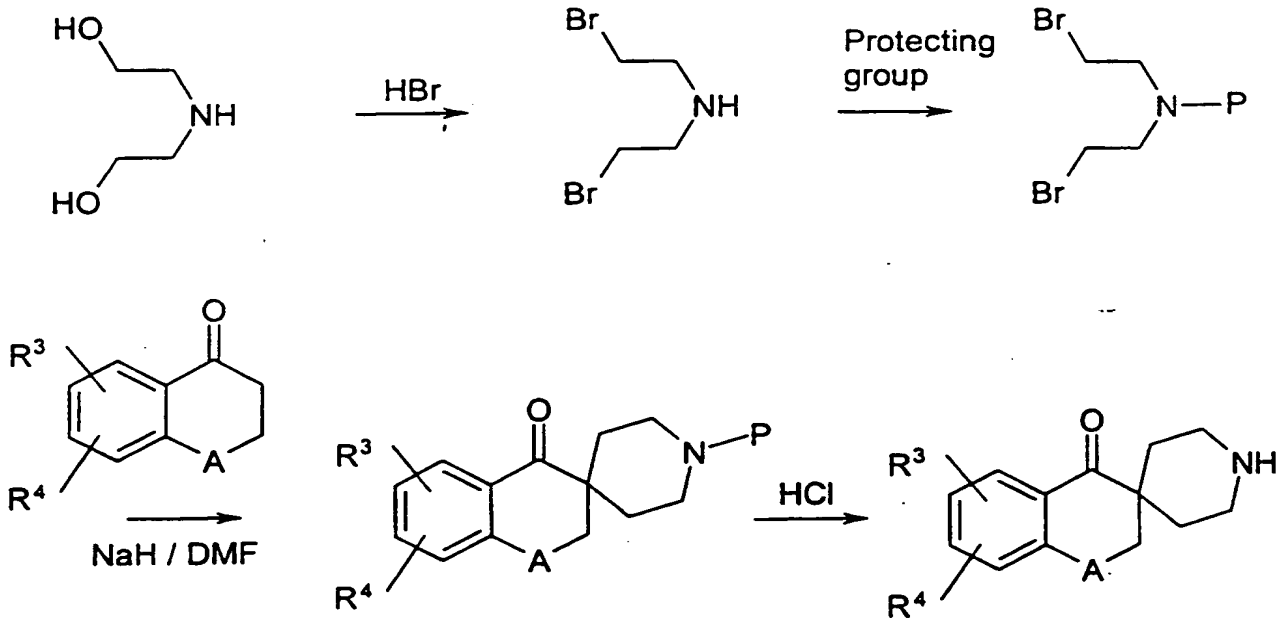
where R^1 , R^2 , R^3 , R^4 , and A have the meanings given above, and " L " is a normal leaving group (e.g. halo such as chloro or bromo, or a silyl derivative such as trimethylsilyl).

The foregoing reaction is carried out by combining approximately equimolar quantities of the spiro amine with the alkylating or acylating agent (i.e. L-R^5), generally in an unreactive organic solvent such as tetrahydrofuran, dimethylsulfoxide, or N,N-dimethylformamide. A base such as triethylamine or $NaHCO_3$ can be utilized to act as an acid scavenger if desired. The reaction typically is substantially complete after about 2 - 20 h, when conducted at a temperature is about 25°C to about 60°C. The product is readily isolated by removing the reaction solvent, and further purification can be achieved if desired by normal means such as salt formation, crystallization, and chromatography.

The required starting material, i.e. the spiro amine, can be synthesized from readily available reactants, utilizing any of several methods:

-In one method, an N-protected form of a derivatized diethylamine is reacted with a bicyclic ketone according to scheme 2:

Scheme 2

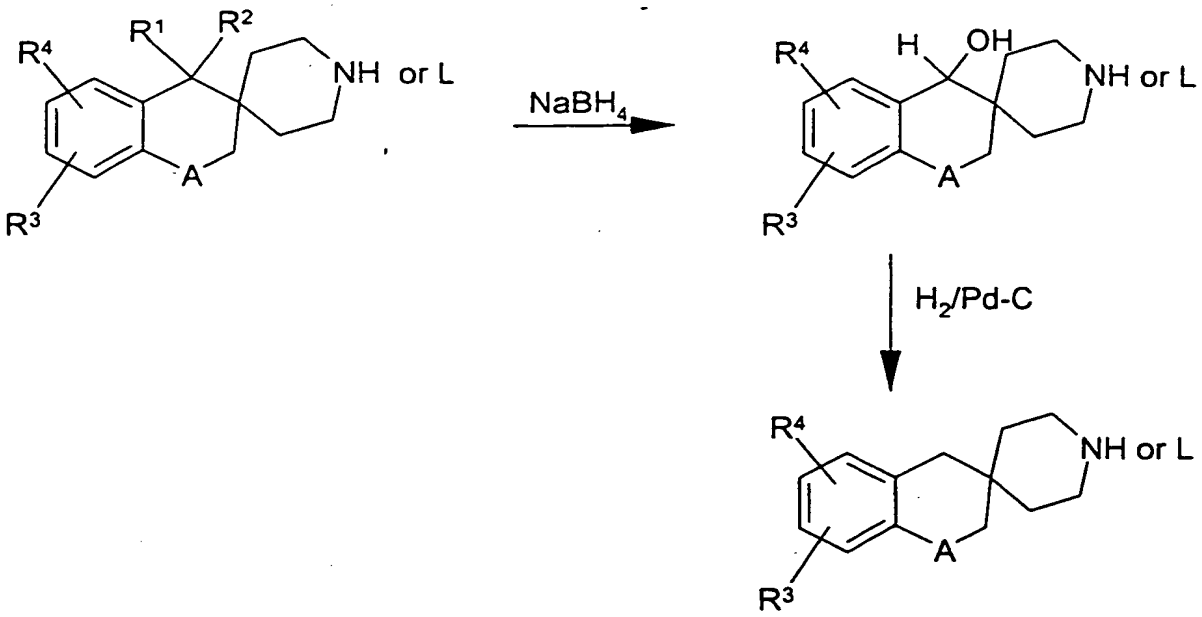


In the above scheme 2, P is an amine-protecting group that is easily removed, for example ethoxycarbonyl or benzyl. The protected diethylamine derivative is readily reacted with a bicyclic ketone in the presence of a strong base such as NaH. This reaction results in formation of the spiro amino derivative, which is readily de-protected by conventional means, for instance by reaction with hydrochloric acid.

Scheme 2 illustrates the preparation of keto substituted starting materials, i.e. where R^1 and R^2 together are oxo. Such compounds are easily converted to the corresponding alcohol (R^1 is H , R^2 is OH) by reaction with a reducing agent such as $NaBH_4$, generally in a solvent such as methanol or ethanol.

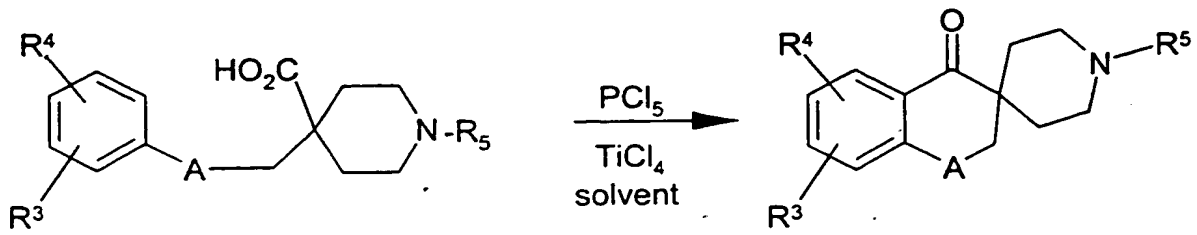
The alcohol can be further reduced by catalytic hydrogenation, for example by reaction with hydrogen gas in the presence of 10% palladium on carbon. These reactions are illustrated in Scheme 3 :

Scheme 3



The invention compounds of Formula I can alternatively be prepared by starting with a suitably substituted piperidine derivative, as shown in Scheme 4 :

Scheme 4

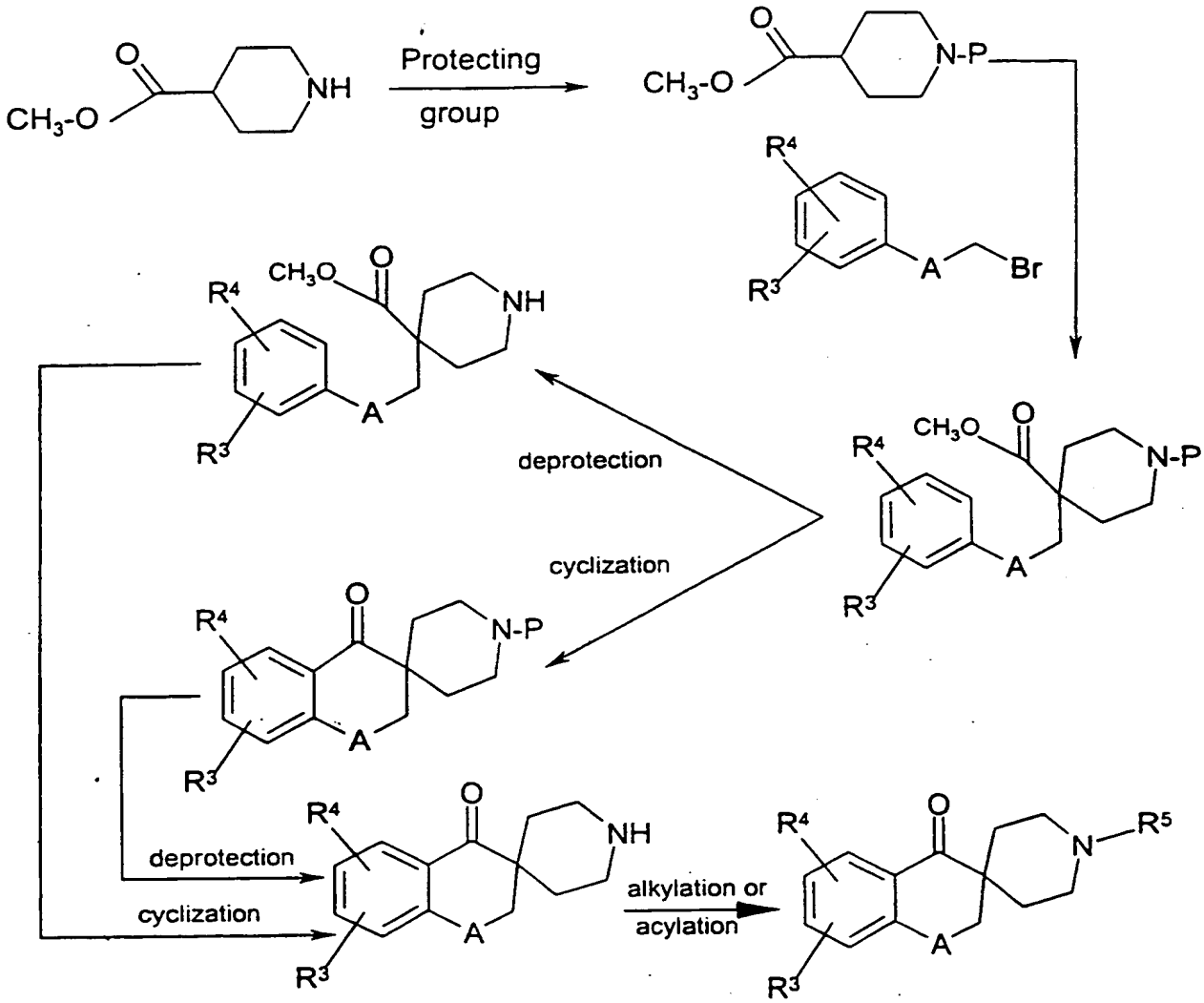


The cyclization reaction is accomplished by reacting the substituted piperidine with strong dehydrating agents such as phosphorus pentachloride and titanium tetrachloride, generally in an unreactive organic solvent such as benzene, toluene, xylene, or chloroform. The reaction normally is complete within 2 h when carried out at a temperature of 30°C to 60°C.

The cyclized product is a compound of Formula I wherein R^1 and R^2 together are oxo, which, as noted above in Scheme 3, can be reduced to the corresponding alcohol or alkane (R^1 and R^2 both hydrogen).

The substituted piperidine required for the above reaction is readily prepared as shown in Scheme 5:

Scheme 5



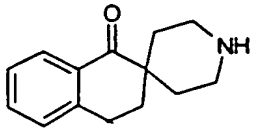
In Scheme 5, the methyl 4-piperidine formate is reacted with an amine-protecting agent (i.e. to insert P). Typical amine-protecting groups include *tert*-butoxy carbonyl, benzyl and trimethylsilyl. The protected piperidine derivative is next

reacted with a phenyl alkyl halide, for example phenylethyl bromide (where A is CH_2) or 2-phenylpropyl iodide (where A is $CH\text{-}CH_3$) or 3-phenylpropyl iodide (where A is $CH_2\ CH_2$), in the presence of a strong base such as NaH or lithium diisopropylamide (LDA), generally in an unreactive solvent such as tetrahydrofuran, or benzene. The reaction, carried out at about –20°C, generally is substantially complete after about 2 - 4 h. The alkylated piperidine can then be deprotected (removal of the L-protecting group) and cyclized by reaction with PCl_5 and $TiCl_4$, or it can be cyclized first, and the L-protecting group subsequently removed.

The following detailed examples illustrate the synthesis of specific compounds provided by this invention. The examples are representative only, and are not intended to be limiting in any respect.

EXAMPLE 1

3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Stage 1: Bis(2-bromoethyl)amine hydrobromide.

157.5 g (1.5 mol) of diethanolamine and then, with stirring, 1.35 l of 48% HBr (exothermic reaction) are introduced into a 2 l three-necked flask which can be equipped either for reflux or for distillation. The solution is heated at a bath temperature of 180-200°C, in order to distill off a volume of 350 ml at a vapour temperature of 122°C. The device is adjusted to the reflux position and is maintained for 1 h. A further distillation is carried out as above, in order to collect a distillate of 465 ml. The device is again adjusted for reflux for 3.75 h and then 400 ml are distilled off. The mixture is cooled and 300 ml of ethyl acetate are added to the residue. The suspension is stirred for 1 h in an ice bath. The precipitate is filtered off and then washed with ethyl acetate. 367 g of a white crystalline product are obtained. Yd = 78.5%, M.p. (°C) = 130-135°C.

Stage 2: Ethyl bis(2-bromoethyl)carbamate.

367 g (1.17 mol) of the product obtained in the preceding stage and then 108 ml, i.e. 122.6 g (1.13 mol), of ethyl chloroformate are added, with stirring, to a 4 l reactor containing 1.8 l of a water/ice mixture. Approximately 1.3 l of a 2N sodium hydroxide solution are run into the solution over 5 min in order to achieve a continuing pH of 11, while maintaining a temperature below 5°C. The mixture is stirred for 5 min and then acidified to pH 1 with concentrated HCl. Extraction is carried out with 3 times 1 l of ethyl ether. The organic phase is washed with 3 times 500 ml of demineralized water and then dried over Na_2SO_4. The solvent is evaporated. The residue is chromatographed by eluting with CH_2Cl_2. 208.5 g of product are obtained. Yd = 58%, TLC (CH_2Cl_2): R_f = 0.6,

N.M.R.: $CDCl_3$ ^1H ((ppm): 1.2 (t, 3H), 3.4-3.55 (m, 4H), 3.6-3.7 (m, 4H), 4.1-4.2 (q, 2H)).

Stage 3: Ethyl 3,4-dihydro-1-oxospiro [naphthalene-2(1*H*),4'-piperidine]-1'-carboxylate.

69 g (0.472 mol) of 1-tetralone and 234 ml of DMF, dried beforehand over molecular sieve, are introduced into a reactor which is protected from moisture and which is under an inert atmosphere. The solution is cooled to -15°C with a dry ice/acetone bath and 34.6 g (1.15 mol) of 80% sodium hydride, as a dispersion in mineral oil, are added thereto. The temperature is allowed to rise to approximately 20-25°C (exothermic reaction). The reaction mixture is stirred for 1.5 h at a temperature below 30°C.

At the same time, a solution of 208 g (0.69 mol) of ethyl bis(2-bromoethyl)carbamate in 234 ml of DMF (dried beforehand over molecular sieve) is cooled, in a reactor which is protected from moisture and which is under an inert atmosphere, to -25°C with a dry ice/acetone bath. The reaction liquors, prepared at the same time, are introduced by transfer under nitrogen and run in over 10 min at a temperature of -25°C. The temperature is allowed to rise (exothermic reaction with rise in the temperature to 45°C). The reaction mixture is then cooled in order to maintain it at approximately 30°C. It is subsequently

brought to 50°C for 2 h and then the solvent is evaporated at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 1.2 l of ice-cold water and extracted with 3 times 600 ml of ether. The organic phase is washed with 3 times 500 ml of demineralized water and then dried over Na_2SO_4. After evaporating the solvent, a dark brown oily residue is obtained which is purified by fast chromatography by eluting with CH_2Cl_2 gradually enriched with acetone. 57.7 g (0.2 mol) of product are obtained (Yd = 42.5%), TLC (97/3 CH_2Cl_2/acetone): R_f = 0.45.

N.M.R.: $CDCl_3$ ^1H ((ppm): 1.15 (t, 3H), 1.4 (m, 2H), 1.8-2.0 (m, 4H), 2.85-2.95 (m, 2H), 3.45-3.55 (m, 4H), 4.0-4.1 (q, 2H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.35 (dd, 1H), 7.9 (d, 1H)).

Stage 4: 3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine).

57.7 g (0.2 mol) of ethyl 3,4-dihydro-1-oxospiro-[naphthalene-2(1*H*),4'-piperidine]-1'-carboxylate and then 1.6 l of 6N HCl are introduced into a reactor. The mixture is stirred and brought to reflux for 14 h. It is then cooled and extracted with twice 500 ml of ethyl ether. The aqueous phase is basified while cold with NaOH and extracted with 3 times 500 ml of ethyl ether. The organic phase is washed and dried over Na_2SO_4. After evaporating the solvent, the residue is purified by chromatography by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH.

Weight: 31 g, Yd = 72%, TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.2-0.35.

N.M.R.: $CDCl_3$ ^1H ((ppm) Base: 1.35-1.45 (m, 2H), 1.8-1.9 (m, 2H), 2.0 (t, 2H), 2.1 (s, 1H), 2.75-2.85 (m, 2H), 2.85-3.0 (m, 4H), 7.1 (d, 1H), 7.2 (dd, 1H), 7.35 (dd, 1H), 7.9 (d, 1H)).

The hydrochloride is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the product in CH_2Cl_2. The mixture is concentrated to dryness and then the product is crystallized from a methanol/ether mixture.

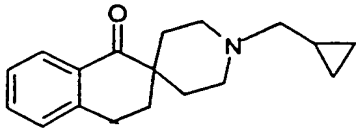
White powder, M.p. = 235°C, TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): $R_f = 0.35$.

Analysis conforms to $C_{14}H_{18}ClNO$.

IR: 2995, 2700, 1675, 1600, 1440, 1395, 1210, 1090, 990, 750, 740 cm^{-1}

EXAMPLE 2

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



10 g (46.4 mmol) of 3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] and then 80 ml of DMF and 36.2 ml of THF are introduced into a three-necked flask. 6.89 g (51 mmol) of (bromomethyl)cyclopropane and 7.8 g (92.8 mmol) of $NaHCO_3$ are added. The suspension is brought to reflux and then maintained for 1.5 h. The solvents are evaporated at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 200 ml of water and extracted with 3 times 100 ml of ether. The ethereal phase is extracted with 100 ml of 1N HCl and then twice with 50 ml of water. The aqueous phase is basified while cold with concentrated NaOH and extracted 3 times with 100 ml of ether. The organic phase is washed with an NaCl solution and dried over Na_2SO_4. Once the solvent has been evaporated, 12 g of an oily residue are obtained. The hydrochloride is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the crude product in CH_2Cl_2. The mixture is concentrated to dryness and then the product is crystallized by addition of 20 ml of ether to a methanolic solution of the product, crystallization is allowed to take place overnight at 20-25°C and then the product is filtered off and washed with water. After drying, 8.4 g of product are obtained.

White powder, M.p. = 243°C, TLC (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): $R_f = 0.55$.

Analysis conforms to $C_{18}H_{24}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.55 (m, 2H), 0.75-0.8 (m, 2H), 1.3-1.4 (m, 1H), 2.1-2.2 (m, 4H), 2.4-2.55 (m, 2H), 2.85-2.9 (m, 2H), 3.0-3.05 (m, 2H), 3.2-

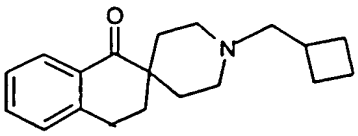
3.3 (m, 2H), 3.5-3.6 (m, 2H), 7.2-7.25 (m, 1H), 7.3-7.35 (m, 1H), 7.5-7.6 (m, 1H), 7.95-8.0 (m, 1H), 12.0-12.2 (m, 1H).

IR: 2990, 2700, 1675, 1600, 1420, 1395, 1320, 1080, 980, 900, 760, 740 cm^{-1}

The corresponding iodomethylate was also obtained. MP: 162°C

EXAMPLE 3

1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The method described for Example 2, using cyclobutylmethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = 235°C.

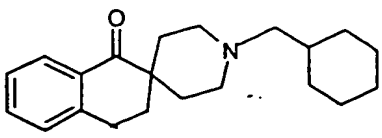
TLC: (92/8 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.7. Analysis conforms to $C_{19}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 1.8-2.25 (m, 10H), 2.4-2.5 (m, 2H), 2.95-3.1 (m, 5H), 3.1-3.25 (m, 2H), 3.25-3.35 (m, 2H), 7.2-7.35 (m, 2H), 7.45-7.55 (m, 1H), 7.9-8.0 (m, 1H), 11.95-12.15 (m, 1H))

IR: 3400, 2900, 2650, 2500, 1680, 1590, 1430, 1360, 1300, 1220, 1140, 1100, 1040, 960, 930, 900, 800, 770, 740, 640 cm^{-1}

EXAMPLE 4

1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The method described for Example 2, using cyclohexylmethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = 265°C.

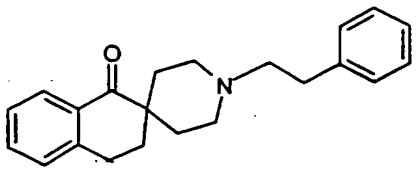
TLC: (93/7 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.8. Analysis conforms to $C_{21}H_{30}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.95-1.3 (m, 5H), 1.6-2.1 (m, 10H), 2.5-2.65 (m, 2H), 2.7-2.8 (m, 2H), 2.9-3.0 (m, 2H), 3.1-3.2 (m, 2H), 3.3-3.4 (m, 2H), 7.15-7.3 (m, 2H), 7.4-7.5 (m, 1H), 7.9-7.95 (m, 1H), 11.6-11.8 (m,1H))

IR: 3400, 2900, 2500, 1680, 1600, 1440, 1360, 1300, 1220, 1150, 1110, 1060, 980, 910, 760, 735 cm^{-1}

EXAMPLE 5

1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The method described for Example 2, using phenethyl bromide, results in the product in the hydrochloride form. Beige powder, M.p. = >275°C, Yd = 55%.

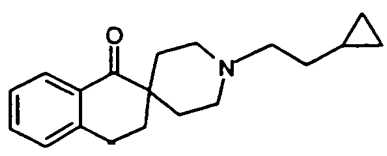
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.85. Analysis conforms to $C_{22}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 2.0-2.15 (m, 4H), 2.3-2.45 (m, 2H), 2.9-3.0 (m, 2H), 3.05-3.25 (m, 6H), 3.4-3.5 (m, 2H), 7.1-7.3 (m, 7H), 7.4-7.45 (m, 1H), 7.85-7.9 (m, 1H), 12.25-12.45 (m, 1H))

IR: 3400, 2900, 2500, 1670, 1600, 1450, 1360, 1290, 1220, 1110, 1010, 960, 820, 800, 740, 700 cm^{-1}

EXAMPLE 6

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



0.94 g (4.36 mmol) of 3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] and then 10 ml of DMF are introduced into a three-necked flask. 1.3 g (8.7 mmol) of (bromoethyl)cyclopropane in 2 ml of DMF and then 0.73 g (8.7 mmol) of $NaHCO_3$ are added to the solution obtained. The suspension is brought to reflux and then maintained for 1.5 h. The solvents are removed at 50°C under a vacuum of less than 1 mm Hg. The residue is taken up in 50 ml of water and extracted with three times 50 ml of ether. The ethereal phase is extracted with 100 ml of 1N HCl and then twice with 50 ml of water. The aqueous phase is basified while cold with concentrated NaOH and extracted 3 times with 50 ml of ether. The organic phase is washed with an NaCl solution and dried over Na_2SO_4. The solvent is removed. The oily residue is purified by fast chromatography by eluting with CH_2Cl_2 enriched with methanol. 0.6 g is obtained, the hydrochloride of which is prepared by addition of approximately 5N ethereal hydrochloric acid to a solution of the crude product in CH_2Cl_2. The mixture is concentrated to dryness and then the product is crystallized by addition of 30 ml of ether to a solution of the product in 5 ml of isopropanol. Crystallization is allowed to take place for 14 h at 20-25°C and then the product is filtered off and washed with ether. After drying, 0.5 g of white powder is obtained, M.p. = 244°C,

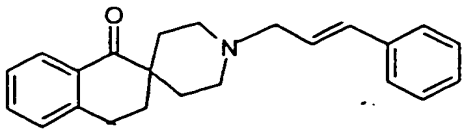
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.35. Analysis conforms to $C_{19}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.1-0.3 (m, 2H), 0.45-0.65 (m, 2H), 0.7-0.8 (m, 1H), 1.6-2.6 (m, 8H), 2.9-3.5 (m, 8H), 7.2-7.4 (m, 2H), 7.4-7.6 (t, 1H), 7.9-8.05 (d, 1H), 12.15 (1H))

IR: 2900, 2450, 1670, 1600, 1430, 1290, 1220, 950, 890, 740 cm^{-1}

EXAMPLE 7

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Prepared according to the method described in Example 2 with cinnamyl bromide, then purification by chromatography and crystallization of the hydrochloride. White powder, M.p. = 228°C.

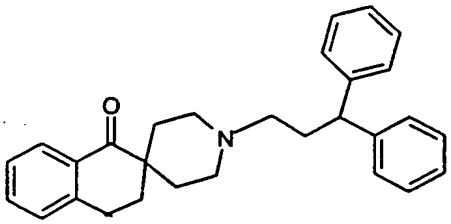
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.55. Analysis conforms to $C_{23}H_{26}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 2.0-2.25 (m, 4H), 2.3-2.5 (m, 2H), 2.9-3.85 (m, 8H), 6.4-6.6 (m, 1H), 6.6-6.8 (d, 1H), 7.1-7.6 (m, 8H), 7.9-8.0 (d, 1H), 12.1 (1H))

IR: 2900, 2400, 1670, 1590, 1420, 1290, 1220, 970, 730, 690 cm^{-1}

EXAMPLE 8

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



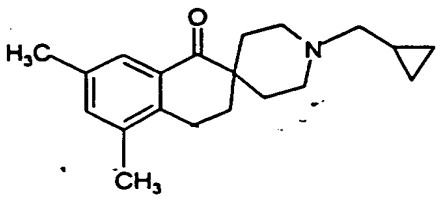
Prepared according to the method described in Example 6 with 3,3-diphenylpropyl bromide and preparation of the hydrochloride. A white powder is obtained, M.p. = 257°C, TLC (95/5 CH_2Cl_2/MeOH): R_f = 0.35. Analysis conforms to $C_{29}H_{32}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 2.0-2.2 (m, 4H), 2.4-3.5 (m, 12H), 3.9-4.05 (m, 1H), 7.2-7.4 (m, 12H), 7.4-7.6 (m, 1H), 7.9-8.0 (m, 1H), 12.3 (1H))

IR: 2900, 2350, 1670, 1590, 1450, 1300, 1220, 910, 740, 700 cm-^{1}

EXAMPLE 9

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] is prepared according to the methods described for the synthesis of Example 1. The "N" alkylation is identical to that described in Example 6. The hydrochloride is obtained in the form of a white powder, M.p. > 260°C.

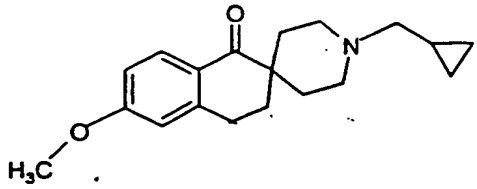
TLC: (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.5. Analysis conforms to $C_{20}H_{28}ClNO$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.3-0.4 (m, 2H), 0.7-0.8 (m, 2H), 1.1-1.3 (m, 1H), 2.0-2.1 (m, 4H), 2.2 (s, 3H), 2.3 (s, 3H), 2.35-2.45 (m, 2H), 2.7-2.85 (m, 4H), 3.0-3.2 (m, 2H), 3.4-3.5 (m, 2H), 7.15 (s, 1H), 7.6 (s, 1H), 12.15 (1H))

IR: 3400, 2900, 2500, 1670, 1605, 1470, 1430, 1280, 1180, 1020, 970, 950, 880, 830 cm^{-1}

EXAMPLE 10

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



By the process of Example 9, the hydrochloride is obtained.

White powder, M.p. > 255°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.35.

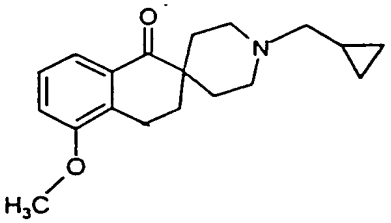
Analysis conforms to $C_{19}H_{26}ClNO_2$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-2.95 (m, 2H), 2.95-3.05 (m, 2H), 3.2-3.4 (m, 2H), 3.45-3.6 (m, 2H), 3.85 (s, 3H), 6.7 (s, 1H), 6.85 (d, 1H), 7.9-8.0 (d, 1H), 12.15 (1H))

IR: 2900, 2420, 1660, 1590, 1430, 1250, 1220, 960, 830, 600 cm^1

EXAMPLE 11

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Same process as for Example 10; the hydrochloride is obtained.

White powder, M.p. = 244°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.75.

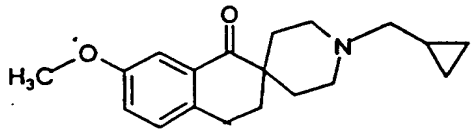
Analysis conforms to $C_{19}H_{26}ClNO_2$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-3.0 (m, 4H), 3.1-3.3 (m, 2H), 3.5-3.6 (m, 2H), 3.85 (s, 3H), 7.0-7.1 (m, 1H), 7.25-7.35 (m, 1H), 7.5-7.6 (m, 1H), 12.1-12.2 (1H))

IR: 2930, 2560, 2360, 1680, 1580, 1470, 1435, 1260, 1060, 970, 750 cm^{-1}

EXAMPLE 12

1'-(methylcyclo-propyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



By using the same methods as for Example 10, the hydrochloride is obtained.

White powder, M.p. = 235°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.70-0.75.

Analysis conforms to $C_{19}H_{26}ClNO_2$.

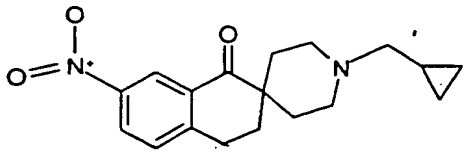
N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.75-0.85 (m, 2H), 1.25-1.4 (m, 1H), 2.05-2.2 (m, 4H), 2.35-2.5 (m, 2H), 2.8-3.0 (m, 4H), 3.2-3.3 (m, 2H), 3.5-3.6

(m, 2H), 3.80 (s, 3H), 7.0-7.1 (m, 1H), 7.15-7.25 (m, 1H), 7.4 (s, 1H), 12.1-12.2 (1H))

IR: 2930, 2510, 2445, 1670, 1610, 1495, 1415, 1250, 1025 cm^{-1}

EXAMPLE 13

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Stage 1: 2.4 g (8.35 mmol) of ethyl 3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]-1'-carboxylate, prepared according to the method described in Stage 3 of Example 1, and 35 ml of concentrated sulphuric acid are introduced into a three-necked flask. 0.79 g (12.5 mmol) of fuming nitric acid is added to the solution cooled to 0°C. The mixture is stirred for 1 h at 0°C and then for 2 h at 20-25°C. The solution is precipitated from 100 ml of water and ice and then extracted with three times 100 ml of CH_2Cl_2. The organic phase is washed successively with water and saturated NaCl solution. After drying over Na_2SO_4 and evaporating the solvent, 2.75 g of an oil are obtained, which oil is chromatographed by eluting with CH_2Cl_2 gradually enriched with acetone. 1.5 g of ethyl 3,4-dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*), 4'-piperidine]-1'-carboxylate are obtained in the form of an oily residue which crystallizes. Yd = 54%, TLC (98/2 CH_2Cl_2/acetone): Rf = 0.3.

N.M.R.: $CDCl_3$ ^1H ((ppm): 1.15 (t, 3H), 1.4 (m, 2H), 1.8-2.0 (m, 4H), 2.9-3.0 (m, 2H), 3.45-3.55 (m, 4H), 4.0-4.1 (q, 2H), 7.3 (d, 1H), 8.2 (d, 1H), 8.8 (s, 1H))

Stage 2: 1.5 g of the product of the preceding stage is hydrolysed by the process described in Stage 4, Example 1. After chromatography, by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH, 0.45 g is isolated. TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.1.

Stage 3: 0.22 g (0.845 mmol) of 3,4-dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] obtained in the preceding stage is suspended in 3 ml of acetonitrile. A solution of 0.343 g (2.54 mmol) of cyclopropylmethyl bromide in 0.5 ml of acetonitrile is added with stirring. The reaction mixture is brought to reflux and maintained for approximately 5 h.

The solvent is removed and the residue is taken up in 20 ml of CH_2Cl_2 and extracted with 20 ml of N/1 HCl. The acidic phase is basified while cold with a dilute sodium hydroxide solution to pH 12 and extracted with 3 times 20 ml of CH_2Cl_2. After washing, drying and removing the solvent, the residue is chromatographed by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH. 0.130 g of 3,4-dihydro-1'-(cyclopropylmethyl)-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine] is obtained. TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.7.

The hydrochloride is prepared as described above. White powder, M.p. = 256°C.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.7.

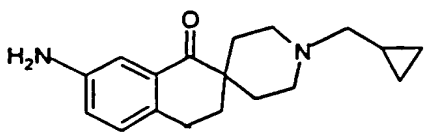
Analysis conforms to $C_{18}H_{23}ClN_2O_3$.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.7-0.8 (m, 2H), 1.2-1.4 (m, 1H), 2-2.25 (m, 4H), 2.4-2.6 (m, 2H), 2.8-2.9 (m, 2H), 3.05-3.3 (m, 4H), 4.5-4.6 (m, 2H), 7.45 (d, 1H), 8.3 (d, 1H), 8.8 (s, 1H), 12.1 (1H))

IR: 2940, 2500, 2440, 1690, 1610, 1520, 1410, 1345, 1220, 1105, 960 cm^{-1}

EXAMPLE 14

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



60 mg (0.19 mmol) of 3,4-dihydro-1'-(methylcyclo-propyl)-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine], obtained as described in Example 13, are dissolved in 1 ml of THF and then, with stirring, 0.21 g of tin chloride hydrate is introduced. The solution is brought to reflux for 1 h. The reaction liquors are charged to a saturated $NaHCO_3$ solution and extracted with 3 times CH_2Cl_2. The organic phase is washed and dried over Na_2SO_4. The solvent is evaporated and the residue obtained is chromatographed by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH. 29 mg of product are obtained.

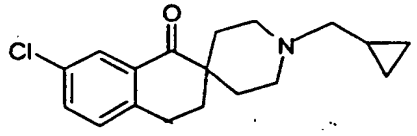
N.M.R.: $CDCl_3$ ^1H ((ppm): 0.1-0.2 (m, 2H), 0.4-0.55 (m, 2H), 0.85-1.0 (m, 1H), 1.6-1.7 (m, 2H), 1.9-2.1 (m, 4H), 2.3-2.4 (m, 2H), 2.5-2.75 (m, 4H), 2.8-2.9 (m, 2H), 3.6-3.8 (2H), 6.8 (d, 1H), 7.0 (d, 1H), 7.2 (s, 1H))

The hydrochloride is crystallized from ether. 26 mg of a yellow powder are obtained.

M.p. = 200°C, decomposition. TLC (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.45.

EXAMPLE 15

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



Stage 1: Piperidine-1,4-dicarboxylic acid, 4-ethyl 1-*t*-butyl diester.

60 g (0.381 mol) of ethyl isonipecotate and 400 ml of THF are placed in a three-necked flask which is protected from moisture and which is under an inert atmosphere, and 18.3 g (0.458 mol) of sodium hydroxide pellets are added. A solution of 100 g (0.458 mol) of di-*t*-butyl dicarbonate in 170 ml of THF is added over 1 h with stirring to the suspension. The temperature reaches 45°C. The reaction mixture is left stirring for 14 h at 20-25°C and is then poured onto 2 l of water and ice and extracted with 3 times 500 ml of ether. The organic phase is washed with 3 times 250 ml of a saturated NaCl solution, dried over Na_2SO_4 and concentrated. The residue is chromatographed by eluting with CH_2Cl_2 gradually

enriched with acetone and then distilled under a vacuum of 0.09 mm Hg and at a vapour temperature of 95-102°C. 82 g are obtained (Yd = 83.6%). TLC (95/5 CH_2Cl_2/acetone): Rf = 0.60.

N.M.R.: $CDCl_3$ ^1H ((ppm): 1.2-1.3 (t, 3H), 1.4 (s, 9H), 1.5-1.6 (m, 2H), 1.8-1.9 (m, 2H), 2.35-2.45 (m, 1H), 2.7-2.85 (m, 2H), 3.9-4.0 (m, 2H), 4.05-4.15 (q, 2H))

Stage 2: 4-(4-Chlorophenethyl)piperidine-1,4-dicarboxylic acid, 4-ethyl 1-*t*-butyl diester

6.16 g (60.9 mmol) of diisopropylamine and 174 ml of THF, dried over molecular sieve, are introduced, by transfer under nitrogen, into a three-necked flask which is protected from moisture and which is under an inert atmosphere. The solution is cooled to -10°C and 24.3 ml of 2.5N *n*-butyllithium in hexane (60.9 mmol) are run in. The mixture is stirred for 15 min at -10°C and cooled to -70°C, and a solution of 10.4 g (40.6 mmol) of the product from the preceding Stage 1 in 86 ml of THF is run in over approximately 20 min. The mixture is stirred for 10 min at -70°C and then 10.9 g (60.9 mmol) of HMPT are added. The mixture is kept stirring at -70°C for 1.5 h and a solution of 4-chlorophenethyl bromide (10.7 g, 48.7 mmol) in 86 ml of THF is run in over 20 min at -70°C. The mixture is stirred at 20-25°C for 14 h and then poured over 350 ml of water and extracted 3 times with ether. The organic phase is washed with an N/1 HCl solution and then with a saturated NaCl solution. After drying and concentrating, 17 g of an orange oil are obtained, which oil is chromatographed by eluting with CH_2Cl_2 gradually enriched with hexane, and then with acetone. 11.8 g are obtained (Yd = 80%). TLC (95/5 CH_2Cl_2/acetone): Rf = 0.70.

NMR: $CDCl_3$ ^1H ((ppm): 1.2-1.3 (t, 3H), 1.4 (s, 9H), 1.3-1.4 (m, 2H), 1.7-1.8 (m, 2H), 2.0-2.1 (m, 2H), 2.3-2.4 (m, 2H), 2.7-2.9 (m, 2H), 3.7-3.9 (m, 2H), 4.05-4.15 (q, 2H), 6.9-7.0 (m, 2H), 7.1-7.2 (m, 2H))

Stage 3: Ethyl 4-(4-chlorophenethyl)piperidine-4-carboxylate

10.8 g of the product from the preceding Stage 2 and 50 ml of CH_2Cl_2 are introduced into a three-necked flask which is protected from moisture. The solution is stirred and 25 ml of trifluoroacetic acid are added at 20-25°C. The mixture is kept stirring for 30 min and then concentrated to dryness and the

residue is taken up in ether. The organic phase is washed with a 10% sodium hydroxide solution and then with a saturated NaCl solution. After drying and concentrating, 9 g of an oil are obtained, which oil crystallizes.

TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.45.

NMR: $CDCl_3$ ^1H ((ppm): 1.1-1.25 (t, 3H), 1.3-1.4 (m, 2H), 1.7-1.8 (m, 2H), 2.1-2.2 (m, 2H), 2.35-2.45 (m, 2H), 2.6-2.7 (m, 2H), 2.9-3.0 (m, 2H), 3.3 (1H), 4.1-4.2 (q, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

Stage 4: Ethyl 1-(cyclopropylmethyl)-4-(4-chlorophenethyl)piperidine-4-carboxylate

3.4 g (11.5 mmol) of the product from the preceding Stage 3, 85 ml of THF, dried over molecular sieve, and then, with stirring, 14.9 ml of triethylamine and 2.4 ml (20.9 mmol) of 85% (bromomethyl)cyclopropane are successively introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. The mixture is brought to reflux for 14 h and then concentrated to dryness, and the residue is taken up in water and extracted twice with ether. The organic phase, washed with a saturated NaCl solution and dried, is concentrated. 3 g of crude product are obtained, which product is chromatographed (eluent: CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH). 2.6 g of oily product are obtained. Yd = 65%.

TLC (95/5 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.50.

N.M.R.: $CDCl_3$ ^1H ((ppm): 0.0-0.1 (m, 2H), 0.35-0.45 (m, 2H), 0.7-0.8 (m, 1H), 1.1-1.2 (t, 3H), 1.4-1.5 (m, 2H), 1.7-1.8 (m, 2H), 1.9-2.1 (m, 2H), 2.1-2.2 (m, 2H), 2.3-2.4 (m, 2H), 2.7-2.85 (m, 2H), 4.1-4.2 (q, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

Stage 5: 1-(Cyclopropylmethyl)-4-(4-chlorophenethyl)-piperidine-4-carboxylic acid

2.2 g (6.28 mmol) of the preceding ester and 6.6 ml of anhydrous dimethyl sulphoxide are introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. A solution of potassium *t*-butoxide (4.4 g, 39 mmol) in 30 ml of dimethyl sulphoxide is added with stirring. The mixture is

left stirring for 2 h at 20-25°C. The reaction mixture is charged to 200 ml of water and then washed with ether. The aqueous phase is acidified to pH 5-7 with 10% HCl. The precipitate is filtered off and washed with water. The acid obtained is crystallized from a CH_2Cl_2/methanol mixture. M.p. = 250°C.

NMR: $CDCl_3$ ^1H ((ppm): 0.2-0.3 (m, 2H), 0.5-0.6 (m, 2H), 1.07-1.1 (m, 1H), 1.6-1.9 (m, 4H), 2.25-2.35 (m, 2H), 2.5-2.6 (m, 2H), 2.65-2.75 (m, 2H), 2.8-2.9 (m, 2H), 3.3-3.4 (m, 2H), 6.9-7.0 (dd, 2H), 7.1-7.2 (dd, 2H))

IR: 3370, 1490, 1445, 1380, 1240, 1170, 1095, 965, 805 cm^{-1}.

Stage 6: 7-Chloro-3,4-dihydro-1'-(cyclopropylmethyl)-1-oxospiro[naphthalene-2(1*H*),4'-piperidine].

0.3 g (0.9 mmol) of the acid obtained previously and 6 ml of benzene are introduced into a round-bottomed flask which is protected from moisture and which is under nitrogen. 0.24 g of PCl_5 and 6 ml of CH_2Cl_2 are added, followed by a further 0.24 g of PCl_5. The mixture is stirred for 2 h at 20-25°C. The mixture is cooled to 0°C, 0.44 ml of tin tetrachloride is introduced (copious precipitation), 12 ml of CH_2Cl_2 are added and the mixture is maintained at 0°C for 1 h and then at 20-25°C for 14 h. The solvents are removed and the residue is taken up in water. The aqueous phase is washed with ether and then basified to pH 12 with NaOH and extracted with ether. The organic phase is washed, dried and concentrated. The crude product is chromatographed by eluting with CH_2Cl_2 gradually enriched with methanol containing 10% NH_4OH. 22 mg of product are obtained, which product is treated in solution in CH_2Cl_2 with 5N ethereal hydrochloric acid. After crystallization from ethyl acetate, the product is filtered off and dried at 50°C under vacuum.

White powder. TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): Rf = 0.55. M.p. = 263°C.

N.M.R.: $CDCl_3$ ^1H ((ppm) HCl: 0.4-0.5 (m, 2H), 0.7-0.8 (m, 2H), 1.2-1.3 (m, 1H), 2.0-2.15 (m, 4H), 2.4-2.55 (m, 2H), 2.8-2.9 (m, 2H), 2.95-3.05 (m, 2H), 3.1-3.3 (m, 2H), 3.5-3.6 (m, 2H), 7.2-7.3 (m, 1H), 7.4-7.5 (m, 1H), 7.9 (s, 1H), 12.2 (1H))

IR: 2930, 2440, 1720, 1490, 1230, 1185, 1095, 1025, 810 cm^{-1}.

EXAMPLES 16-34

Following the general procedures described above, the following additional compounds listed in table 1 were prepared.

Table 1

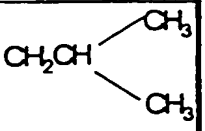
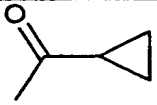
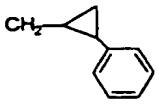
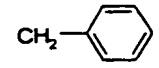
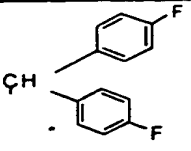
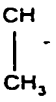
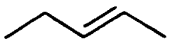
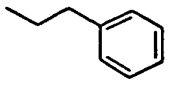
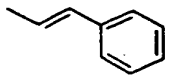
Example	R^1	R^2	R^3	R^4	A	R^5
16	=O		H	H	CH_2	CH_3
17	=O		H	H	CH_2	$CH_2CH=CH_2$
18	=O		H	H	CH_2	
19	=O		H	H	CH_2	
20	=O		H	H	CH_2	

Table 1 (cont.)

Example	R^1	R^2	R^3	R^4	A	R^5
21	=O		H	H	CH_2	
22	=O		H	H	CH_2	
23	H	OH	H	H	CH_2	

24	H	H	H	H	CH_2	
25	=O		H	H	Bond	
26	=O		H	H	CH_2CH_2	
27	=O		H	H		
28	=O		6-Cl	H	CH_2	
29	=O		6-F	H	CH_2	
30	=O		$6:OCH_3$	$7:OCH_3$	CH_2	
31	=O		H	H	CH_2	
32	=O		H	H	CH_2	
33	=O		H	H	CH_2	
34	=O		$6:OCH_3$	H	CH_2	

MP and NMR data for the compounds of examples 16 to 34 are provided below:

Example 16

MP = 240-243°C

R.M.N. $CDCl_3$ ^1H δ (ppm) Base:1,5-1,6 (m,2H); 1,95-2,05 (m,4H); 2,25 (s,3H); 2,3-2,4 (m,2H); 2,45-2,55 (m,2H); 2,9-2,95 (m,2H); 7,1-7,15 (m,1H); 7,2 - 7,25(m,1H); 7,35-7,4 (m,1H); 7,9-7.95 (m,1H)

Example 17

MP = 242-244°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl:2,05-2,15 (m,4H); 2,3-2,45 (m,2H); 3,0-3,1 (m,2H); 3,1-3,25 (m,2H); 3,35-3,5 (m,2H); 3,55-3,6 (m,2H); 5,4-5,55 (m,2H); 6,1 -6,25(m,1H); 7,2-7,35 (m,2H); 7,45-7.5 (m,1H); 7,9-7,95 (m,1H); 12,3-12,45 (m,1H)

Example 18

MP = 244-245°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 1,15 (d,6H); 2,0-2,1 (m,4H); 2,15-2,3 (m,1H); 2,55-2,65 (m,2H); 2,75-2,8 (m,2H); 2,95-3,0 (m,2H); 3,1-3,25 (m,2H); 3,35-3,45 (m,2H);7,2-7,35 (m,2H); 7,45-7.5 (m,1H); 7,9-7,95 (m,1H); 11,7-11,8 (m,1H)

Example 19

MP = 95-97°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: 0,6-0,7 (m,2H); 0,8-0,95 (m,2H); 1,4-1,5 (m,2H); 1,6-1,7 (m,1H); 1,8-2,1 (m,4H); 2,9-3,5 (m,2H); 3,4-3,8 (m,4H); 7,1-7,3 (m,2H); 7,35-7.45 (m,1H); 7,9-8,0 (m,1H);

Example 20

MP = 220-221°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 1,05-1,3 (m,2H); 1,5-1,9 (m,1H); 2,0-2,2 (m,5H); 2,3-2,55 (m,2H); 2,9-3,4 (m,6H); 3,4-3,6 (m,2H); 7,0-7,6 (m,8H); 7,9-8,1 (m,1H); 12,2-12,4 (m,1H)

Example 21

MP = 261-262°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 2,0-2,1 (m,4H); 2,4-2,5 (m,2H); 2,95-3,05 (m,2H); 3,1-3,25 (m,2H); 3,3-3,4 (m,2H); 4,1-4,15 (m,2H); 7,2-7,35 (m,2H); 7,4-7,5 (m,4H); 7,65-7,7 (m,2H); 7,9-7,95 (m, 1H); 12,25-12,5 (m,1H)

Example 22

MP = > 250°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: 1,4-1,55 (m,2H); 1,9-2,05(m,4H); 2,2-2,35 (m,2H); 2,4-2,55 (m,2H); 2,8-2,95 (m,2H); 4,2 (s,1H); 6,8-7,0 (m,4H); 7,15 (d,1H); 7,2-7,35 (m,5H); 7,4 (t,1H); 7,9 (d ,1H)

Example 23

MP = 91-93°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: -0,05-0,05 (m,2H); 0,35-0,45(m,2H); 0,7-0,85 (m,1H); 1,25-1,85 (m,7H); 2,2 (d,2H); 2,2-2,4 (m,2H); 2,5-2,6 (m,1H); 2,6-2,7 (m,3H); 4,2 (s,1H); 7,0- 7,3 (m ,4H)

Example 24

MP = 256-258°C

R.M.N. $CDCl_3$ ^1H δ (ppm) base: 0,0-0,1 (m,2H); 0,4-0,5(m,2H); 0,75-0,85 (m,1H); 1,45-1,55 (m,4H); 1,6-1,65 (m,2H); 2,2 (d,2H); 2,35-2,6 (m,6H); 2,7-2,8 (m,2H); 6,9- 7,05 (m ,4H)

Example 25

MP= 241°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,0-0,15 (m,2H); 0,4-0,55 (m,2H); 0,75-0,9 (m,1H); 1,35 (d,2H); 1,9-2,15 (m,4H); 2,25 (d,2H); 2,9 (s,2H); 3,0 (d,2H); 7,25 (t,1H); 7,35 (d 1H); 7,5 (t,1H); 7,65 (d,1H); 12,1-12,2 (1H)

Example 26

MP = 242-243°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,7-0,8 (m,2H); 1,2-1,35 (m,1H); 1,85-2,0 (m,4H); 2,2-2,3 (m,2H); 2,3-2,4 (m,2H); 2,7-2,9 (m,6H); 3,4-3,5 (m,2H); 7,15-7,4 (m,4H);12,1-12,3 (1H)

Example 27

MP = 234°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,45 (m,2H); 0,75 (m,2H); 1,35 (m,1H); 1,4(dd,3H); 1,85 (m,2H); 2,1 (m,3H); 2,3 (m,1H); 2,75 (m,2H); 2,9 (m, 2H) 3,25 (m,1H); 3,45-3,8 (m,3H); 7,3-7,45 (m,2H);7,6 (m,1H); 8,0 (dd,1H); 12,1 (1H)

Example 28

MP = > 250°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,75-0,85 (m,2H); 1,3-1,4 (m,1H); 2,1-2,2 (m,4H); 2,4-2,55 (m,2H); 2,9-2,95 (m,2H); 3,0-3,05 (m, 2H); 3,2-3,3 (m,2H); 3,5-3,6 (m,2H); 7,25-7,3 (m,2H);7,9,7,95 (m,1H); 12,2 (1H)

Example 29

MP = 227°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,4-0,5 (m,2H); 0,75-0,85 (m,2H); 1,3-1,4 (m,1H); 2,0-2,2 (m,4H); 2,4-2,6 (m,2H); 2,85-2,95 (m,2H); 3,0-3,1 (m, 2H); 3,2-3,3 (m,2H); 3,5-3,6 (m,2H); 6,9-7,0 (m,1H); 7,0-7,1 (m,1H); 7,95-8,05 (m,1H); 12,1 (1H)

Example 30

MP = 229°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,45 (m,2H); 0,75 (m,2H); 1,35 (m,1H); 2,15 (m,4H); 2,45 (td,2H); 2,9 (m,2H); 2,95 (m, 2H); 3,3 (m,2H); 3,55 (m,2H); 4,85 (s,3H); 4,95 (s,3H); 6,65 (s,1H); 7,45 (s,1H); 12,05 (1H)

Example 31

M P = 189-192°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 0,2-0,3 (m,1H); 0,6-0,7 (m,1H); 0,7-0,8 (m,1H); 0,8-0,9 (m,1H); 1,1-1,2 (m,1H); 1,55 (d,3H); 1,6-1,7 (m,1H); 2,1-2,2 (m,4H); 2,5-2,7 (m,2H); 3,0-3,1 (m,2H); 3,3-3,6 (m,4H); 7,2-7,25 (m,1H); 7,3-7,35 (m,1H); 7,45-7,5 (m1H); 8,0-8,05 (m,1H); 11,85 (1H)

Example 32

M P = > 235°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 1,7 (d,3H); 2,1-2,2 (m,4H); 2,4-2,5 (m,2H); 2,6-2,7 (m,2H); 2,9-3,1 (m,4H); 3,2-3,3 (m,2H); 3,4-3,5 (m,2H); 5,3-5,4 (m,1H);5,6-5,7 (m,1H); 7,2-7,3 (m,1H); 7,3-7,35 (m,1H); 7,5-7,6 (m1H); 7,95-8,0 (m,1H); 12,2 (1H)

Example 33

M P = 209°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 2,1 (m,4H); 2,25 (m,2H); 2,45 (m,2H); 2,7 (m,2H); 2,9 (m, 2H); 3,0 (m,2H); 3,15 (m,2H); 3,4 (m,2H); 7,1-7,35 (m,7H); 7,5 (m,1H); 7,95 (m,1H); 11,95 (1H)

Example 34

M P = 228°C

R.M.N. $CDCl_3$ ^1H δ (ppm) HCl: 2,0-2,2 (m,4H); 2,4 (td,2H); 3,0 (m,2H); 3,3 (qd, 2H); 3,45 (m,2H); 3,75 (t,2H); 3,85 (s,3H); 6,55 (qt,1H); 6,7 (m,2H); 6,85 (dd,1H); 7,35 (m,3H); 7,45 (d,2H); 7,95 (d,1H); 11,95 (1H).

EXAMPLES 35-69

Following procedures known in the art, some of the tetralones described above were alkylated to yield the following additional compounds listed in table 2.

Table 2

Ex.	R^1-R^2	R_3	R_4	R_5	A	Rf
35	=O	5:OCH_3	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.7
36	=O	5:OCH_3	H	CH_2-c-C_4H_7	CH_2	0.5
37	=O	5:OCH_3	H	CH_2-c-C_6H_{11}	CH_2	0.8
38	=O	5:OCH_3	H	CH_2-CH=CH-C_6H_6	CH_2	0.7
39	=O	5:OCH_3	H	CH_2-CH_2-C_6H_6	CH_2	0.7

40	=O	5:OCH_3	H	CH_2-CH_2-CH_2-C_6H_6	CH_2	0.55
41	=O	5:OCH_3	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.90
42	=O	6:OCH_3	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.4
43	=O	6:OCH_3	H	CH_2-c-C_4H_7	CH_2	0.3
44	=O	6:OCH_3	H	CH_2-c-C_6H_{11}	CH_2	0.55
45	=O	6:OCH_3	H	CH_2-CH=CH-C_6H_6	CH_2	0.5
46	=O	6:OCH_3	H	CH_2-CH_2-C_6H_6	CH_2	0.5
47	=O	6:OCH_3	H	CH_2-CH_2-CH_2-C_6H_6	CH_2	0.4
48	=O	6:OCH_3	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.7
49	=O	7:OCH_3	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.5
50	=O	7:OCH_3	H	CH_2-c-C_4H_7	CH_2	0.2
51	=O	7:OCH_3	H	CH_2-c-C_6H_{11}	CH_2	0.4
52	=O	7:OCH_3	H	CH_2-CH=CH-C_6H_6	CH_2	0.4
53	=O	7:OCH_3	H	CH_2-CH_2-C_6H_6	CH_2	0.4
54	=O	7:OCH_3	H	CH_2-CH_2-CH_2-C_6H_6	CH_2	0.3
55	=O	7:OCH_3	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.65

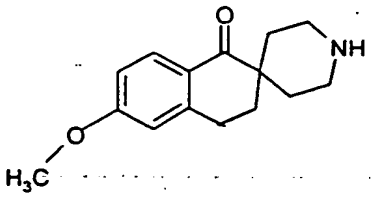
Table 2 (cont.)

Ex. .	R^1-R^2	R_3	R_4	R_5	A	Rf
56	=O	H	H	$(CH_2)_2$-c-C_3H_5	$CHCH_3$	0.4
57	=O	H	H	CH_2-c-C_4H_7	$CHCH_3$	0.2
58	=O	H	H	CH_2-c-C_6H_{11}	$CHCH_3$	0.5
59	=O	H	H	CH_2-CH=CH-C_6H_6	$CHCH_3$	0.45
60	=O	H	H	CH_2-CH_2-C_6H_6	$CHCH_3$	0.5
61	=O	H	H	CH_2-CH_2-CH_2-C_6H_6	$CHCH_3$	0.4
62	=O	H	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	$CHCH_3$	0.7
63	=O	6:Cl	H	$(CH_2)_2$-c-C_3H_5	CH_2	0.5

64	=O	6:Cl	H	CH_2-c-C_4H_7	CH_2	0.3
65	=O	6:Cl	H	CH_2-c-C_6H_{11}	CH_2	0.65
66	=O	6:Cl	H	CH_2-CH=CH-C_6H_6	CH_2	0.55
67	=O	6:Cl	H	CH_2-CH_2-C_6H_6	CH_2	0.65
68	=O	6:Cl	H	CH_2-CH_2-CH_2-C_6H_6	CH_2	0.5
69	=O	6:Cl	H	$(CH_2)_2$-CH-$(C_6H_6)_2$	CH_2	0.85

EXAMPLE 70

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]



The synthesis is similar to the one described in example 1 except in stage 3 wherein 6-methoxytetralone is used instead of 1-tetralone.

N.M.R.: $CDCl_3$ ^1H ((ppm) Base: 1.9-2.3 (m, 6H); 2.9-3.1 (m, 2H); 3.3-3.6 (m, 4H); 3.85 (s, 3H); 6.65 (s, 1H); 6.8-6.9 (m, 1H); 7.9-8.0 (dd, 1H); 9.5 (bs, 2H)).

M.P. = 236-237°C, TLC (90/10 CH_2Cl_2/MeOH containing 10% NH_4OH): R_f = 0.25.

IR: 2724, 1657, 1595, 1446, 1258, 1223, 1086, 978, 906, 839 cm^{-1}

As noted above, the invention compounds of Formula I are useful for treating chronic pain and other CNS disorders such as seizures, e.g. epilepsy. The compounds have been evaluated in standard assays to measure their ability to block isolated mammalian Na neuronal channels, as well as their ability to antagonize prostaglandin E_2 (PGE_2) production. Both assays are routinely utilized to indicate clinical utility of compounds for treating chronic pain and other CNS disorders (see Tonelian *et al.*, Anesthesiology, 24: 949-951, 1991).

EXAMPLE 71

Sodium channel [^{3}H]-batrachotoxin (BTX) binding assay

Cerebral cortices from male Sprague-Dawley rats were homogenized in a glass-Teflon homogenizer in 10 volumes of ice-cold 0.32 M sucrose, 5 mM K_2HPO_4 (pH 7.4 at 4°C). The homogenate was centrifuged at 1000 g. for 10 min, the pellet was resuspended in the same volume of sucrose and recentrifuged. The pellet was discarded and the two supernatants resulting from these two centrifugations were pooled and centrifuged at 20000 g. for 10 min. The resulting pellet was resuspended in a Na-free assay buffer containing 50 mM HEPES, 5.4 mM KCl, 0.8 mM $MgSO_4$, 5.5 mM glucose and 130 mM choline chloride (pH 7.4 at 25°C). Binding assay were initiated by the addition of 150-200 µg synaptosomal protein to an assay buffer containing 25 µg scorpion venom (Leirus quinquestriatus), 0.1% BSA and 10 nM [^{3}H] batrachotoxin (40 Ci/mmol, NEN) in the presence or absence of different concentrations of unabelled drugs (250 µl final volume). Non-specific binding was determined in the presence of 0.3 mM veratridine. Reactions were incubated for 90 min at 25°C and bound ligand was separated from free by vacuum filtration through Whatman GF/B filters; the filters were washed with 2x5 ml buffer (5 mM HEPES, 1.8 mM $CaCl_2$, 0.8 mM $MgSO_4$, 130 mM choline chloride, 0.01% BSA ; pH 7.4 at 25°C) and bound ligand was estimated by liquid scintillation spectrometry.

EXAMPLE 72

$^{22}Na^+$ influx into SK-N-SH neuroblastoma cells

Characterization of Na^+ channels activity is performed using human SK-N-SH cells in 96-well culture plates. The effect of tested compounds on Na^+ influx through the Na^+ channels is evaluated under stimulation by veratridine.

SK-N-SH cells are preincubated for 15 min at 37°C in the presence of test compounds in a 25 mM hepes/Tris pH 7.5 buffer containing 5.4 mM KCl, 0.8 mM $MgSO_4$, 1.8 mM $CaCl_2$, 5mM glucose, 0.1% BSA, 140 mM choline chloride.

The influx of Na^+ is induced by the incubation for 10 min at 37°C of SK-N-SH cells in the presence of test compound and veratridine in the incubation buffer supplemented with 1 µM ouabaine, 10 mM NaCl, 130 mM choline chloride and $^{22}Na^+$ (Jacques, Y, Fosset, M. and Lazdunski, M., (1978), Molecular properties of the action potential Na+ ionophore in neuroblastoma cells. J. Biol. Chem., 253, 7383-7392).

Following this $^{22}Na^+$ uptake, cells are washed with 0.1 mM $MgCl_2$. The radioactivity is then measured with a microplate reader (Topcount, Packard) after the addition of a scintillation liquid (Microscint 40, Packard).

The reference compound is tetrodotoxin tested at 7 concentrations ranging from 10^{-10}M to 10^{-7} M in order to determine an IC_{50} value.

EXAMPLE 73

Analgesic activity on chronic hyperalgesia induced by PGE_2 in rats

The test consists in determining the analgesic effect of the test compound in rats by the Randall and Selitto test, in which chronic hyperalgesia has been triggered by intraplantar injection of PGE_2 over 4 days into a leg, according to a protocol adapted from Nakamura-Craig *et al* (Pain, **63**: 33-37, 1995).

The study is carried out on batches of 120-140 g Sprague-Dawley rats to which 100 ng of PGE_2 is administered in a volume of 100 µl by the intraplantar route, for 4 consecutive days twice a day; this causes chronic hyperalgesia in the leg from the 5th day, for at least one week. On the day of the test, in the morning, the threshold of reaction to pain is checked by the Randall and Selitto test, and animals whose threshold is ψ100 arbitrarily defined units are selected. In the afternoon, the measurement is repeated after prior administration by the s.c. route of a solution of the test compound; this administration is carried out 30 min before measuring the pain threshold. For each batch, the analgesic activity (%) is

calculated from the means of the thresholds measured before and after treatment, as compared with that of the control animals, who received only the vehicle.

The following Table 3 lists the Na channel binding and the analgesic activities of representative compounds of the invention when measured in the foregoing assays.

Table 3: Pharmacological activities

Compound of Example No	[^{3}H] BTX assay: Na^+ channel binding Ki (nM)	^{22}Na influx IC50 (µM)	PGE_2 assay: Analgesic activity at 10 mg/kg S.C. (%)
2	876	10.7	49
6	1435	3.4	67
7	366	0.94	57
8	397	0.97	47
10	3890	30	100
33	291	1.2	81
36	475	3.4	51
42	ND	4.3	46
43	ND	6	39
47	ND	0.6	66
49	2183	7.6	38
70	ND	ND	46

The foregoing biological data establish that the compounds of Formula I are particularly useful for treating CNS disorders in mammals, especially neuropathic pain, trigeminal neuralgia, diabetic neuropathy, sciatic neuropathy and seizures. The compounds are particularly well suited to the treatment of diabetic neuropathy, which is the most common complication accompanying diabetes mellitus. The compounds also are useful for prophylaxis and treatment of migraine.

The invention compounds can be administered to humans who are in need of treatment for a chronic pain condition or seizure disorder by both the oral and parenteral routes, for instance as tablets or capsules, or as subcutaneous or intravenous injections. The compounds will be administered in an amount which is effective to control and treat the seizure disorder or relieve the neuropathic pain sensation. Such effective amounts will generally be from about 0.1 to about 2000 mg/kg of mammalian body weight. Commonly prescribed doses will be from about 5 mg/kg to about 500 mg/kg. Such dosage amounts can be administered to adult humans from 1 to 4 times a day for the relief of neuropathic pain and seizure disorders. The precise dose to be employed will depend upon the specific compound of Formula I utilized, the particular condition of the subject being treated, and generally will be dictated by the attending physician or other medical practitioner.

The compounds can be formulated by normal methods for convenient oral or parenteral dosing. Typical oral forms are tablets, capsules, troches, elixirs, syrups, suspensions, and controlled sustained release forms, for example through osmotic pumps. The compounds can likewise be formulated for administration intraperitoneally, subcutaneously, intramuscularly, transdermally, sublingually or intravenously. The compounds are formulated by using conventional diluents, excipients, carriers and binders routinely used in the phamaceutical art. For example, the compounds can be admixed with carriers, diluents and excipients such as starch, cellulose, PVP, methylcellulose, sugar, wax, talc, and with stabiliżers and binders such as Mg stearate, MgO, $CaCO_3$, methyl-*p*-hydroxybenzoate (methylparaben), and *n*-propyl-*p*-hydrobenzoate (propylparaben).

The following additional examples illustrate typical pharmaceutical formulations which are provided by this invention.

EXAMPLE 74

Tablet Preparation

Compound of Example 10	25.0 mg
Microcrystalline cellulose	50.0 mg
Modified food corn starch	50.0 mg
Magnesium stearate	1.0 mg

The above ingredients are blended to uniformity and compressed into a tablet. Such tablets are administered at the rate of 1 to 4 times a day to a human suffering from chronic pain.

EXAMPLE 75

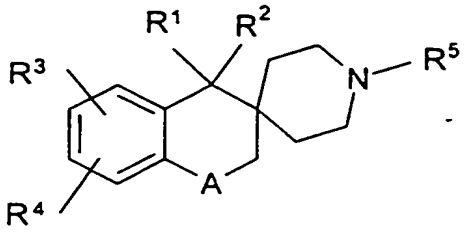
Intravenous Preparation

Compound of example 2	400 mg
Acetate buffer	20 ml
dil aqueous HCl or NaOH	to pH6.5
Sterile isotonic saline	qs 1000 ml

The invention compound is dissolved in the acetate buffer and the pH is adjusted to 6.5. Isotonic saline is added to a volume of 1000 ml. The solution is filled into a sterile flexible plastic container equipped with a drip tube. The solution is administered IV to a patient suffering from diabetic neuropathy.

What is claimed is :

1. A tricyclic compound of Formula I:



(I)

wherein:

R^1 is hydrogen or hydroxy;

R^2 is hydrogen or hydroxy; or

R^1 and R^2 together are oxygen ;

A is a bond, CH_2, CH CH_3, CH_2 CH_2 or $C(CH_3)_2$;

R^3 and R^4 are the same or different and are hydrogen, halo, C_1-C_6 alkyl, C_1-C_4 alkoxy, trifluoromethyl, NO_2, COR^6, $COOR^6$ or NR^6R^7, wherein R^6 and R^7 are the same or different and are hydrogen, C_1-C_6 alkyl or benzyl ;

R^5 is hydrogen, $C_{1\text{-}6}$ alkyl, $C_{2\text{-}6}$ alkenyl, $C_{3\text{-}6}$ cycloalkyl, (O=C)-$C_{1\text{-}6}$ alkyl, (O=C)- $C_{2\text{-}6}$ alkenyl, (O=C)-$C_{3\text{-}6}$ cycloalkyl, wherein said alkyl, alkenyl and cycloalkyl groups can be substituted by 1, 2 or 3 groups selected from halo, C_3-C_6 cycloalkyl, phenyl or substituted phenyl, and a pharmaceutically acceptable salt thereof.

2. A compound according to Claim 1, wherein R^5 is C_1-C_6 alkyl, optionally substituted with phenyl or a C_3-C_6 cycloalkyl group.

3. A compound according to Claim 1 or 2, wherein R^3 is hydrogen, halogen or $C_{1\text{-}4}$ alkoxy.

4. A compound according to any one of Claims 1 to 3, wherein R^1 is C_{1-6} alkyl, C_{2-6} alkenyl or C_{3-6} cycloalkyl, optionally substituted by 1, 2 or 3 groups selected from halo, C_3-C_6 cycloalkyl, phenyl or substituted phenyl, and R^2 is hydrogen.

5. A compound according to any one of Claims 1 to 4, wherein R^4 is hydrogen.

6. A compound selected from the group consisting of:
3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclobutylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclohexylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-phenylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];
1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

3,4-dihydro -1'-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'- allyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(2-methylpropyl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropionyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) - 1' (trans-2-phenyl-methylcyclopropyl) ;

3,4-dihydro -1'-benzyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

3,4-dihydro -1'-(di-p-fluorobenzhydryl)-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine]

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclohexylmethyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(2-phenylethyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclobutylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cyclohexylmethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(2-phenylethyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

7. A compound selected from the group consisting of:

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5,7-dimethyl-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-5-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-7-nitro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Amino-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-7-Chloro-3,4-dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylmethyl- 1,3,4-trihydro -1-hydroxy-spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 1,2,3,4-tetrahydro -spiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl-1,3-dihydro-1-oxospiro-[2H-indene-2,4'-piperidine]

1'-(cyclopropylmethyl)-8,9-dihydrospiro[6H-benzocycloheptene-6,4'-piperidin]-5(7H)-one ;

1'-cyclopropylmethyl- 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

6-chloro-1'-cyclopropylmethyl- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6-fluoro-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-cyclopropylmethyl- 3,4-dihydro -6,7-dimethoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(1-cyclopropyl-1-ethyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine) ;

1'-(3-pentene)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl- 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) -3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl -3,4-dihydro-4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl -3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cinnamyl - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3,3'diphenylpropyl) - 3,4-dihydro -4-methyl-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro-1'-cyclopropylethyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-cinnamyl - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

6-chloro -1'-(3-phenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ; and

6-chloro -1'-(3,3'diphenylpropyl) - 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine.

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

8. A compound selected from the group consisting of :

1'-cyclopropylmethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cyclopropylethyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-cinnamyl-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3,3-diphenylpropyl)-3,4-Dihydro-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(cyclopropylmethyl)-3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine];

1'-(3-phenylpropyl)- 3,4-dihydro -1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -5-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclobutylmethyl - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-(3-phenylpropyl) - 3,4-dihydro -6-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

1'-cyclopropylethyl - 3,4-dihydro -7-methoxy-1-oxospiro(naphthalene-2(1H),4'-piperidine ;

3,4-Dihydro-6-methoxy-1-oxospiro[naphthalene-2(1*H*),4'-piperidine]

9. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 8 admixed with a pharmaceutically acceptable carrier, diluent, or carrier therefor.

10. A method for treating a mammal suffering from pain and in need of treatment comprising administering an effective amount of a compound of any one of Claims 1 to 8.

11. A method according to Claim 10 wherein the pain is neuropathic pain.

12. A method according to Claim 10 wherein the pain is diabetic neuropathy.

13. A method for treating a mammal suffering from a seizure disorder comprising administering an effective amount of a compound of any one of Claims 1 to 8.

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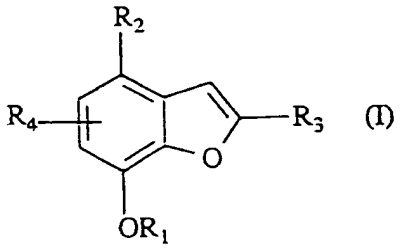
(54) 2-(Piperidin-4-yl, pyridin-4-yl and tetrahydropyridin-4-yl)benzofuran-7-ol and carbamate derivatives, their preparation and their use as acetylcholinesterase inhibitors.

(57) 2-(piperidin-4-yl, pyridin-4-yl and tetrahydropyridin-4-yl)benzofuran-7-ol and carbamate derivatives of the formula I



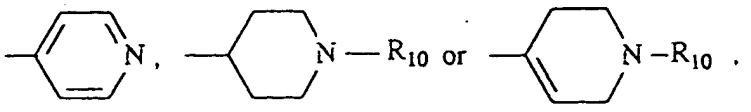
(I)

wherein

R_1 is hydrogen, loweralkyl, arylloweralkyl, $CONHR_5$ or $CONR_6R_7$

R_2 is hydrogen, cyano, $CH_2NR_8R_9$, $CONHR_5$ or $CONR_6R_7$;

R_3 is



where R_{10} is hydrogen, loweralkyl, arylloweralkyl, $CONHR_5$, $CONR_6R_7$, acyl, acyloxyloweralkyl or acyloxyaryllow ralkyl;

R_4 is hydrog n, halogen, loweralkyl or loweralkoxy;

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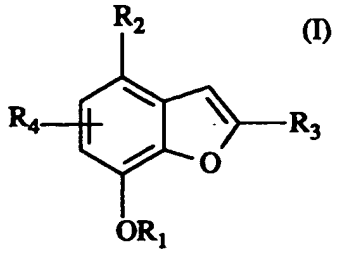
R_5 is hydrogen, loweralkyl or aryllow ralkyl;
R_6 is loweralkyl or aryllow ralkyl;
R_7 is low ralkyl or aryllow ralkyl;
R_8 is hydrogen, loweralkyl, aryllow ralkyl or acyl;
R_9 is hydrogen, loweralkyl or arylloweralkyl;
R_{11} is loweralkyl, aryl or aryloweralkyl;

with the proviso that if R_1 is hydrogen or loweralkyl, R_2 cannot be hydrogen; or a pharmaceutically acceptable acid addition salt thereof, or where applicable, an optical or geometric isomer or racemic mixture thereof, which are useful as acetylcholinesterase inhibitors and as such may be useful for the treatment of Alzheimer's disease and other senile dementias.

The present invention relates to compounds of the general formula



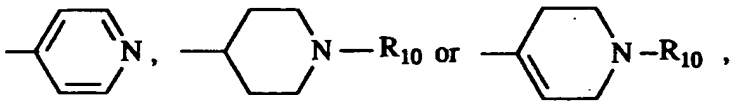
(I)

wherein

R_1 is hydrogen, loweralkyl, aryloweralkyl, $CONHR_{11}$ or $CONR_6R_7$

R_2 is hydrogen, cyano, $CH_2NR_8R_9$, $CONHR_5$ or $CONR_6R_7$;

R_3 is



where R_{10} is hydrogen, loweralkyl, aryloweralkyl, $CONHR_5$, $CONR_6R_7$, acyl, acyloxyloweralkyl or acyloxyaryloweralkyl;

R_4 is hydrogen, halogen, loweralkyl or loweralkoxy;

R_5 is hydrogen, loweralkyl or aryloweralkyl;

R_6 is loweralkyl or aryloweralkyl;

R_7 is loweralkyl or aryloweralkyl;

R_8 is hydrogen, loweralkyl, aryloweralkyl or acyl;

R_9 is hydrogen, loweralkyl or aryloweralkyl;

R_{11} is loweralkyl, aryl or aryloweralkyl;

with the proviso that if R_1 is hydrogen or loweralkyl, R_2 cannot be hydrogen;

or a pharmaceutically acceptable acid addition salt thereof, or, where applicable, an optical or geometric isomer or racemic mixture thereof.

Additionally, this invention also relates to novel intermediates encompassed by the above formula, to pharmaceutical compositions containing said compounds and to their use as acetylcholinesterase inhibitors.

Unless otherwise stated or indicated, the following definitions shall apply throughout the specification and appended claims.

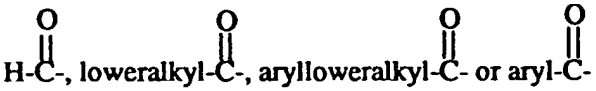
The term "lower" shall mean the group it is describing contains from 1 to 6 carbon atoms.

The term loweralkyl shall mean a straight or branched alkyl group having from 1 to 6 carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and straight and branched chain pentyl and hexyl.

The term halogen shall mean fluorine, chlorine, bromine or iodine.

The term aryl shall mean a phenyl group substituted with 0, 1 or 2 substituents each of which is independently loweralkyl, loweralkoxy, halogen, trifluoromethyl or nitro.

The term acyl shall mean a group of the formula

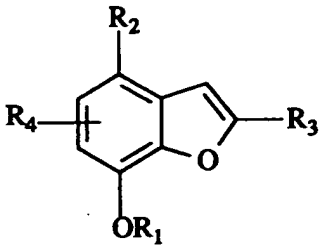


where loweralkyl and aryl are as defined above.

Throughout the specification and appended claims, a given chemical formula or name shall encompass all stereo and optical isomers where such isomers exist.

Additionally, a given chemical formula or name shall encompass the pharmaceutically acceptable addition salts thereof.

In a pr f rred mbodiment of this inv ntion are compounds of th formula

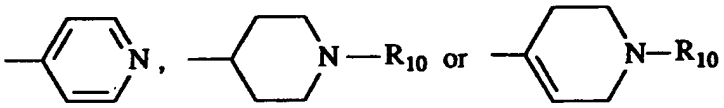


where

R_1 is $CONHR_{11}$ or $CONR_6R_7$;

R_2 is $CH_2NR_8R_9$, $CONHR_5$ or $CONR_6R_7$;

R_3 is



where R_{10} is hydrogen or loweralkyl;

R_4 is hydrogen or halogen;

R_5 is hydrogen or loweralkyl;

R_6 is loweralkyl;

R_7 is loweralkyl;

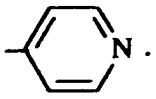
R_8 is hydrogen or loweralkyl;

R_9 is hydrogen or loweralkyl; and

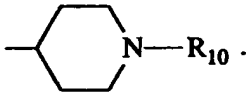
R_{11} is loweralkyl, aryl or aryllowеralkyl.

The following compounds are particularly preferred:

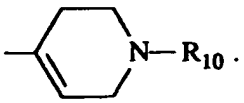
a. A compound of formula I as defined above wherein R_3 is



b. A compound of formula I as defined above wherein R_3 is



c. A compound of formula I as defined above wherein R_3 is



d. A compound as defined under a) wherein R_1 is $CONHR_{11}$.

. Th compound as d fined under d) which is 2-(4-pyridinyl)benzofuran-7-yl methyl carbamate.

f. The compound as defined under d) which is 2-(4-pyridinyl)benzofuran-7-yl butyl carbamate.

g. A compound as defined und r a) wher in R_1 is loweralkyl.

h. Th compound as d fined under g) which is 4-(N,N-diethyl)-7-methoxy-2-(4-pyridinyl)-benzofuranamide.

i. A compound as defined under b) wherein R_1 is $CONHR_{11}$.

j. The compound as defined under i) which is 2-(1-methyl-4-piperidinyl)-benzofuran-7-yl methyl carbamate.

k. A compound as defined under b) wherein R_1 is $CONR_6R_7$.

l. The compound as defined under k) which is 2-(4-piperidinyl)-benzofuran-7-yl dimethyl carbamate.

m. A compound as defined under b) wherein R_1 is loweralkyl.

n. The compound as defined under m) which is 1-methyl-4-(4-N,N-diethylamido-7-methoxy-2-benzofuranyl)piperidinium maleate.

o. The compound as defined under m) which is 1-methyl-4-(4-cyano-7-methoxy-2-benzofuranyl)-piperidinium maleate.

p. The compound as defined under m) which is 1-methyl-4-(4-aminomethyl-7-methoxy-2-benzofuranyl)-piperidine.

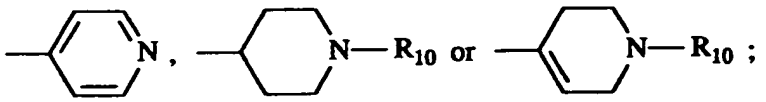
q. The compound as defined under m) which is 1-methyl-4-(4-N,N-diethylaminomethyl-7-methoxy-2-benzofuranyl)piperidine.

Preferred intermediates of this invention are compounds wherein

R_1 is loweralkyl;

R_2 is cyano, $CH_2NR_8R_9$ or $CONR_6R_7$;

R_3 is



R_4 is hydrogen;

R_5 is loweralkyl; and

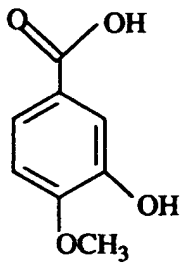
R_6, R_7, R_8, R_9 and R_{10} are loweralkyl.

The compounds of this invention are prepared in the following manner. The substituents R_1 to R_{11} are as defined above unless indicated otherwise.

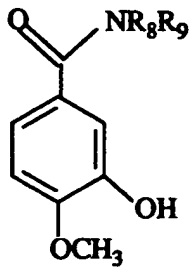
The compounds of this invention can be prepared according to either of the following synthetic routes.

SYNTHETIC ROUTE I

A carboxylic acid of the formula

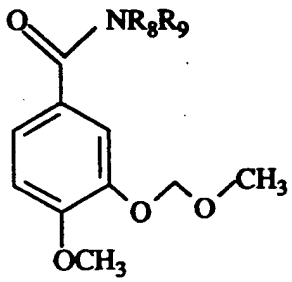


is reacted with thionyl chloride, in a suitable solvent such as toluene, and subsequently reacted with a secondary amine of the formula HNR_8R_9, where R_8 and R_9, are loweralkyl, to yield compound (II) of the formula



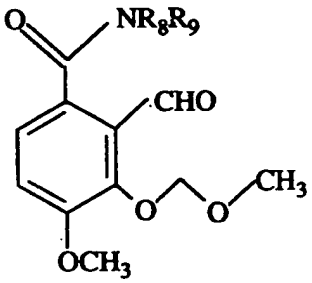
(II)

Compound II is reacted in chloromethyl methyl ether with 50% NaOH in dichloromethane with tetrabutylammonium chloride to afford compound III of the formula



(III)

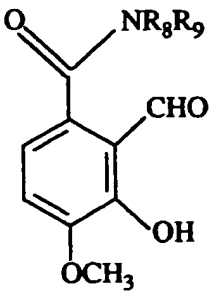
Compound III in THF is subsequently reacted with sec-butyllithium in a suitable solvent such as cyclohexane, and dimethylformamide is added later to afford compound IV of the formula



(IV)

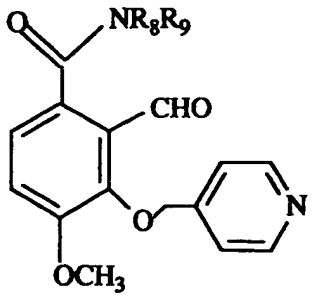
where R_8 and R_9 are ethyl. This reaction is typically conducted at a temperature of -70 to -40 °C for 1 to 4 hours.

Compound IV is hydrolyzed by standard means to afford compound IVa of the formula



(IVa)

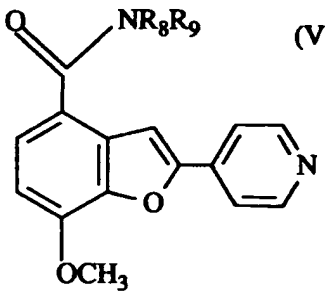
Compound IVa is reacted with 4-picolylchlorid hydrochlorid , potassium carbonate and a catalyst such as potassium iodide to yield Compound V of th formula



(V)

This reaction is typically conducted in a suitable solvent such as dimethylformamide. The reaction mixture is stirred at about 60-100 °C for 1-3 hours and then heated to about 130-170 °C for 10-30 minutes.

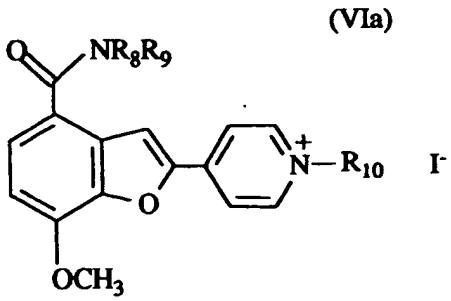
Compound VI of the formula



(VI)

was concomitantly formed in the synthesis of Compound V, and the two compounds were chromatographically separated.

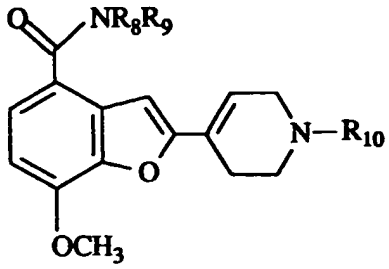
Compound VI is subsequently reacted with methyl iodide in methylethyl ketone or other suitable solvent at a temperature of about 40 to 60 °C to yield Compound VIa of the formula



(VIa)

where R_{10} is methyl. Compound VIa is then treated with a reducing agent such as sodium borohydride or another metallic borohydride in a loweralkanolic solvent such as methanol to give Compound VIb of the formula

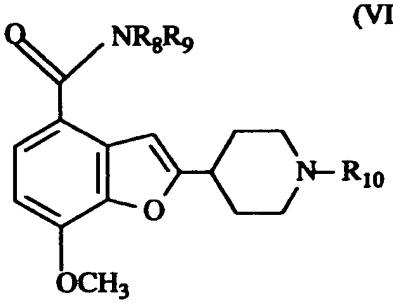
(VIb)



where R_{10} is methyl. This reaction typically takes place at a temperature of about -10 to 100°C for 0.5 to 24 hours.

Compound VIb is subsequently hydrogenated in the presence of a noble metal catalyst and an acid such as hydrogen bromide to prepare compound VII of the formula

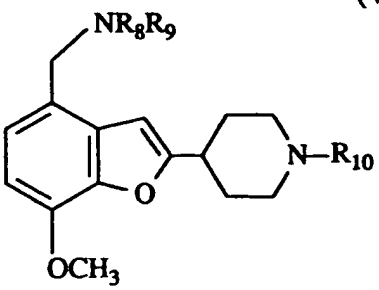
(VII)



where R_{10} is methyl. Preferred noble metal catalysts include palladium, platinum or rhodium. Platinum, in this case, is preferred; in the form of the metal supported on an inert surface such as carbon or as the oxide or salt.

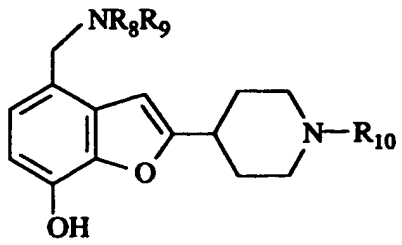
Compound VII is then treated with a reducing agent such as lithium aluminum hydride to yield compound VIII of the formula

(VIII)



where R_{10} is methyl. This reaction typically takes place in a suitable solvent such as tetrahydrofuran at a temperature of about 40 to 60°C for 2 to 4 hours.

Compound VIII is treated with a strong acid, such as 48% HBr, to yield compound IX of the formula

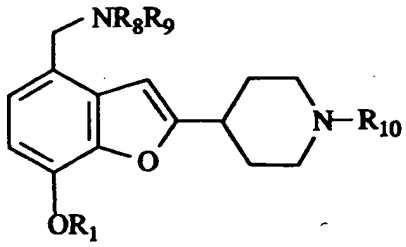


(IX)

where R_{10} is methyl.

Compound IX is subsequently mixed with a catalytic amount of a catalyst such as CuCl or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in a suitable solvent such as dimethylformamide to which is added an isocyanate of the formula $R_{11}NCO$, where R_{11} is loweralkyl, aryl or arylloweralkyl or a carbamoyl chloride of the formula $ClCONR_6R_7$ to afford compound X of the formula

(X)

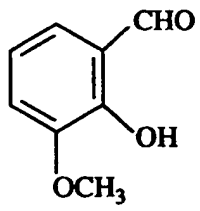


where R_1 is $CONHR_{11}$ or $CONR_6R_7$. This reaction typically takes place under a nitrogen atmosphere at ambient temperature for 12 to 20 hours.

SYNTHETIC ROUTE II

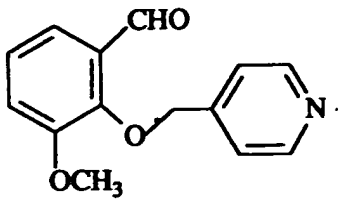
Alternatively, the compounds of this invention can be prepared according to the following synthetic route.

A solution of o-vanillin of the formula



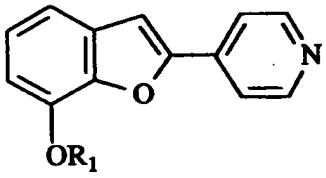
and picolylchloride hydrochloride is reacted with potassium carbonate and potassium iodide in a suitable solvent such as dimethylformamide to afford compound XI of the formula

(XI)



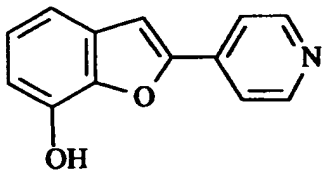
Compound XI is subsequently cyclized by reaction with H_2SO_4 to afford Compound XII of the formula

(XII)



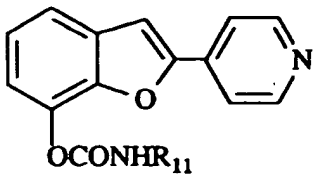
Typically, this reaction takes place in a suitable solvent such as DMF at a temperature of about 120 to 170°C for 6 to 10 hours. Compound XII, where R_1 is loweralkyl, can be reacted with a strong acid such as hydrogen bromide at reflux to prepare compound XIIa

(XIIa)



Compound XIIa is subsequently reacted with an isocyanate of the formula $R_{11}NCO$, where R_{11} is as defined in the previous synthetic route, to afford compound XIII of the formula

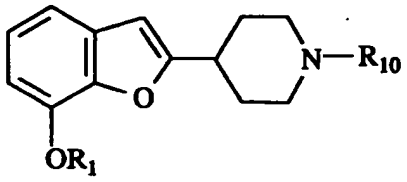
(XIII)



This reaction typically takes place in the presenc of a catalytic amount of a metallic halide, such as CuCl or DBU, and ethyl ac tate at ambient temperatur under nitrogen or other inert gas.

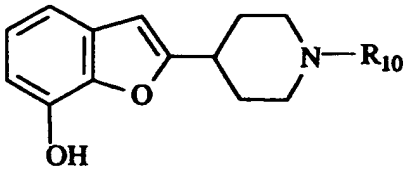
Compound XII, where R_1 is loweralkyl, is reacted as shown in the previous synthetic route to afford the piperidinyl compounds of th formula

(XIV)

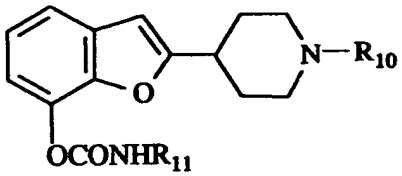


Compound XIV is reacted as previously shown to prepare compounds XIVa and XIVb where R_1 is hydrogen and $CONHR_{11}$, respectively.

(XIVa)



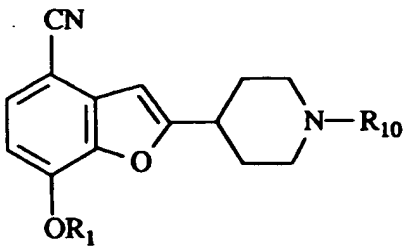
(XIVb)



Alternatively, Compound XIVa can also be reacted with a bicyclic amidine catalyst, such as DBU, with the subsequent addition of an isocyanate of the formula $R_{11}NCO$ to afford compound XIVb. This reaction is typically conducted in a suatable solvent such as acetonitrile under nitrogen at ambient temperature for 2 to 5 hours.

Compound XIV, where R_1 is loweralkyl, is reacted with chlorosulfonylisocyanate under nitrogen to afford Compound XV of the formula

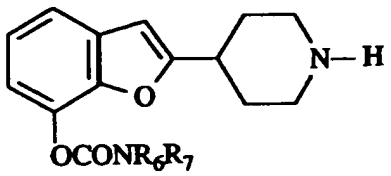
(XV)



This reaction typically takes place in a suitable solvent such as dichloromethane at room temperatur . The reaction mixture is stirred at ambient temperature for 1 to 5 hours and a small porition of dimethylformamide is added and stirring is continued for 12-18 hours.

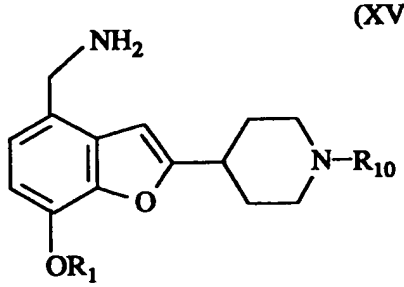
Compound XIVb, where R_{10} is methyl, is reacted with chloroethyl chloroformate in a suitable solvent such as dichloroethane and refluxed for 1 to 12 hours. The mixture is concentrated, then diluted with an alkanolic solvent, such as methanol, and refluxed from 1 to 4 hours to yield compound XIVc of the formula

(XIVc)



Compound XV is treated with lithium aluminum hydride under a nitrogen atmosphere to yield Compound XVI of the formula

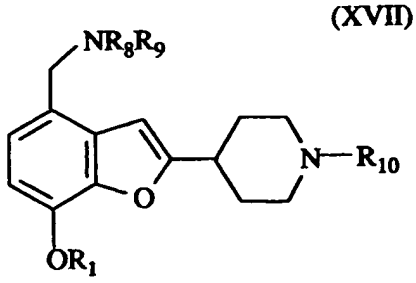
(XVI)



This reaction typically takes place in a suitable solvent such as tetrahydrofuran at ambient temperature for 2 to 6 hours.

Compound XVI can then be treated with a loweralkyl halide or diloweralkyl sulfate to afford Compound XVII of the formula

(XVII)



where R_8 is loweralkyl and R_9 is hydrogen or loweralkyl.

The compounds of the present invention are useful as acetylcholinesterase inhibitors and as such may be useful for the treatment of various memory dysfunctions characterized by a decreased cholinergic function such as Alzheimer's disease.

This utility is manifested by the ability of these compounds to inhibit the enzyme acetylcholinesterase and thereby increase acetylcholine levels in the brain.

Cholinesterase Inhibition Assay

Cholinesterases are found throughout the body, both in the brain and in serum. However, only brain acetylcholinesterase (AChE) distribution is correlated with central cholinergic innervation. This same

inn rvation is sugg sted to be weak ned in Alzh imer patients. W have determined *in vitro* inhibition of acetylcholinesterase activity in rat striatum according to the method described below.

In Vitro Inhibition of Acetylcholinesterase Activity in Rat Striatum

Acetylcholinesterase (AChE), which is sometimes called true or specific cholinesterase, is found in nerve cells, skeletal muscle, smooth muscle, various glands and red blood cells. AChE may be distinguished from other cholinesterases by substrate and inhibitor specificities and by regional distribution. Its distribution in the brain correlates with cholinergic innervation and subfractionation shows the highest level in nerve terminals.

It is generally accepted that the physiological role of AChE is the rapid hydrolysis and inactivation of acetylcholine. Inhibitors of AChE show marked cholinomimetic effects in cholinergically-innervated effector organs and have been used therapeutically in the treatment of glaucoma, myasthenia gravis and paralytic ileus. However, recent studies have suggested that AChE inhibitors may also be beneficial in the treatment of Alzheimer's dementia.

The method described below was used in this invention for assaying anticholinesterase activity. This is a modification of the method of Ellman et al., Biochem. Pharmacol. 7, 88(1961).

Procedure:

A. Reagents

1. 0.05 M Phosphate buffer, pH 7.2
   (a) 6.85 g $NaH_2PO_4 \cdot H_2O$/100 ml distilled H_2O
   (b) 13.40 g $Na_2HPO_4 \cdot 7H_2O$/100 ml distilled H_2O
   (c) add (a) to (b) until pH reaches 7.2
   (d) Dilute 1:10
2. Substrate in buffer
   (a) 198 mg acetylthiocholine chloride (10 mM)
   (b) bring to 100 ml with 0.05 M phosphate buffer, pH 7.2 (reagent 1)
3. DTNB in buffer
   (a) 19.8 mg 5,5-dithiobisnitrobenzoic acid (DTNB) (0.5 mM)
   (b) bring to 100 ml with 0.05M phosphate buffer, pH 7.2 (reagent 1)
4. A 2mM stock solution of the test drug is made up in a suitable solvent and brought to volume with 0.5 mM DTNB (reagent 3). Drugs are serially diluted (1:10) such that the final concentration (in cuvette) is 10^{-4} M and screened for activity. If active, IC_{50} values are determined from the inhibitory activity of subsequent concentrations.

B. Tissue Preparation

Male Wistar rats are decapitated, brains rapidly removed, corpora striata dissected free, weighed and homogenized in 19 volumes (approximately 7 mg protein/ml) of 0.05 M phosphate buffer, pH 7.2, using a Potter-Elvehjem homogenizer. A 25 microliter aliquot of the homogenate is added to 1 ml of vehicle or various concentrations of the test drug and preincubated for 10 minutes at 37 • C.

C. Assay

Enzyme activity is measured with the Beckman DU-50 spectrophotometer. This method can be used for IC_{50} determinations and for measuring kinetic constants.

Instrument Settings

Kinetics Soft-Pac Module #598273 (10)
Program #6 Kindata:
Source - Vis
Wavelength - 412 nm
Sipper - none
Cuvettes - 2 ml cuvettes using auto 6-sampler

Blank - 1 for each substrate concentration
Interval time - 15 seconds (15 or 30 seconds for kinetics)
Total time - 5 minutes (5 or 10 minutes for kinetics)
Plot - y s
Span - autoscale
Slope - increasing
Results - yes (gives slope)
Factor-1 Reagents are added to the blank and sample cuvettes as follows:

Blank:	0.8 ml Phosphate Buffer/DTNB 0.8 ml Buffer/Substrate
Control:	0.8 ml Phosphate Buffer/DTNB/Enzyme 0.8 ml Phosphate Buffer/Substrate
Drug:	0.8 ml Phosphate Buffer/DTNB/Drug/Enzyme 0.8 ml Phosphate Buffer/Substrate

Blank values are determined for each run to control non-enzymatic hydrolysis of substrate and these values are automatically subtracted by the kindata program available on kinetics soft-pac module. This program also calculates the rate of absorbance change for each cuvette.

For IC_{50} Determinations:

Substrate concentration is 10 mM diluted 1:2 in assay yielding final concentration of 5 mM. DTNB concentration is 0.5 mM yielding 0.25 mM final concentration

$$\% \text{ Inhibition} = \left(\frac{\text{slope control - slope drug}}{\text{slope control}}\right)(100)$$

IC_{50} values are calculated from log-probit analysis. Results of this assay for some of the compounds of this invention and a reference compound are presented below in Table 1.

TABLE 1

Compound	Inhibitory Concentration (μM) Brain AChE
2-(1-methyl-4-piperidinyl)benzofuran-7-yl methyl carbamate	1.8
2-(4-pyridinyl)benzofuran-7-yl methyl carbamate	1.2
2-(1-methyl-4-piperidinyl)benzofuran-7-yl diethyl carbamate	1.9
Physostigmine (reference)	0.006

These compounds are administered to a subject who may benefit from the administration of acetylcholinesterase inhibitors at an effective oral, parenteral or intravenous dose of from about 1 to 100 mg/kg of body weight per day. A particularly preferred effective amount is about 10 mg/kg of body weight per day. It is to be understood, however, that for any particular subject, specific dosage regimen should be adjusted according to the individual need and the professional judgment of the person administering or supervising the administration of the compound. It is to be further understood that the dosages set forth herein are exemplary only and do not to any extent limit the scope or practice of the invention.

Effective quantities of the compounds of the present invention may be administered to a subject by any one of various methods, for example, orally as in capsules or tablets, parenterally in th form of st rile solutions or suspensions, and in som cases intravenously in the form of sterile solutions. The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization, increased solubility and the lik .

Pr ferred pharmaceutically acceptable addition salts includ salts of inorganic acids such as hydrochloric, hydrobromic, sulfuric, nitric, phosphoric and perchloric acids; as well as organic acids such as tartaric, citric, acetic, succinic, mal ic, fumaric, and oxalic acids.

The activ compounds of th present invention may be administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be between 4% to about 75% of the weight of the unit. The amount of compound present in such composition is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 mgs of active compound.

The tablets, pills, capsules, troches and the like may also contain the following ingredients: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel™, corn starch and the like; a lubricant such as magnesium stearate or Sterotex®; a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring may be added. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of the aforesaid compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 mgs of active compound.

The solutions or suspensions may also include the following components; a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Examples of possible pharmaceutical formulations such as tablets, suppositories and emulsions are described below:

PHARMACEUTICAL FORMULATIONS

TABLET:

Ingredients	In each tablet
Active ingredient	300 mg
Polyvinylpyrrolidone	22.5 mg
Lactose	61.75 mg
Alcohol 3A - 200 proof	4.5 mg
Stearic acid	9 mg
Talc	13.5 mg
Corn starch	43.25 mg

Blend the active compound, polyvinylpyrrolidone and lactose together and pass through a 40-mesh screen. Add the alcohol slowly, knead w ll; screen the wet mass through a 4-mesh screen and dry the granulation at 50 °C overnight. Screen the dried granulation through a 20-mesh screen. Bolt the st aric acid,

talc and corn starch through a 60-mesh screen prior to mixing by tumbling with th granulation. Compress using 7/16 in. standard concave punch. 10 tablets should w igh 4.5 g.

SUPPOSITORY:

Ingredients	In each suppository
Active ingredient	300 mg
Glycerin	3000 mg
Purified water	200 mg

The glycerin is heated in a suitable container to about 120°C. The drug is dissolved, with gentle stirring, in the heated glycerin after which the purified water is added, mixed and the hot mixture immediately poured into a suitable mold.

EMULSION:

Ingredients	Amount
Gelatin Type A*	4 g
Active Ingredient	360 mg
Flavor as desired	
Alcohol	30 ml
Oil	250 ml
Purified water, to make	500 ml

* prepared from acid-treated precursors; used at a pH of ca. 3.2.

Add the gelatin and the drug to about 300 ml of purified water, allow to stand for a few minutes, heat until the gelatin is dissolved, then raise the temperature to about 98°C, and maintain this temperature for about 20 min. Cool to 50°C, add the flavor, the alcohol, and sufficient purified water to make 500 ml. Add the oil, agitate the mixture thoroughly, and pass it through a homogenizer or a colloid mill until the oil is completely and uniformly dispersed.

Examples of the compounds of this invention include: N,N-Diethyl-2-formyl-4-methoxy-3-(methoxymethylenoxy)benzamide; N,N-diethyl-4-methoxy-2-formyl-3-(4-pyridinylmethoxy)benzamide; 4-(N,N-diethyl)-7-methoxy-2-(4-pyridinyl)benzofuranamide; 1-methyl-4-(4-N,N-diethylamido-7-methoxy-2-benzofuranyl)piperidinium maleate; 1-methyl-4-(4-cyano-7-methoxy-2-benzofuranyl)piperidinium maleate; 1-methyl-4-(4-aminomethyl-7-methoxy-2-benzofuranyl)piperidine dihydrobromide; 1-methyl-4-(4-N,N-diethylaminomethyl-7-methoxy-2-benzofuranyl)piperidine dihydrobromide monohydrate; 2-(1-methyl-4-piperidinyl)-benzofuran-7-yl methyl carbamate; 2-(4-pyridinyl)benzofuran-7-yl methyl carbamate; 2-(4-pyridinyl)benzofuran-7-yl butyl carbamate; Methyl-4-(7-methoxy-2-benzofuranyl)piperidine; 1-methyl-4-(4-N,N-dimethylamino-7-methoxy-2-benzofuranyl)piperdine; 2-(1-methyl-4-piperidinyl)benzofuran-7-yl 1,2,3,4-tetrahydroisoquinolyl carbamate; 2-(4-pyridinyl)-4-N,N-diethylaminobenzofuran-7-yl methyl carbamate; 2-(1-methyl-4-piperidinyl)-4-N,N-dimethylamino-2-benzofuran-7-yl butyl carbamate; and 2-(4-piperidinyl)-benzofuran-7-yl dimethyl carbamate.

The following examples are for illustrative purposes and are not to be construed as limiting the invention disclosed therein. All temperatures are given in degrees centigrade (°C) unless indicated otherwise.

EXAMPLE 1

N,N-DIETHYL-2-FORMYL-4-METHOXY-3-(METHOXYMETHYLENOXY)BENZAMIDE

To a solution of N,N-diethyl-4-methoxy-3-(methoxymethyleneoxy)benzamide (82.0 g) in tetrahydrofuran (hereafter "THF") (800 ml) at -55°C was added a 1.3 M solution of sec-butyl lithium in cycloh xane (307

ml) dropwise during 1 hour. After stirring the mixtur for an additional hour at -55 °C, dim thylformamid (hereafter "DMF"), (36.5 g) was added dropwise. The mixtur was allowed to warm to ambient t mperature and stirred for 2 hours, poured into ice cold 5% HCl, and xtracted twice with thyl acetate. Th combined organic phases w re washed with wat r and brine, dried (Na_2SO_4) and concentrated *in vacuo* t giv 97g of crude product. Preparative high performance liquid chromatography (silica gel, eluting with 1:2 heptane:ethyl acetate) afforded 58 g of the pure product which was crystallized from heptane/acetone, m.p. 75-77 °C.

Analysis:			
Calculated for $C_{15}H_{21}NO_5$:	61.00%C	7.17%H	4.74%N
Found:	60.97%C	7.12%H	4.84%N

EXAMPLE 2a

N,N-DIETHYL-4-METHOXY-2-FORMYL-3-(4-PYRIDINYLMETHOXY)BENZAMIDE

A suspension of N,N-diethyl-4-methoxy-3-(4-pyridinylmethoxy)benzamide (19.0g), 4-picolylchloride hydrochloride (15.0 g), K_2CO_3 (60.0 g) and potassium iodide (5.0 g) in DMF (500 mol) was stirred at 80 °C for 2 hours and then heated to 150 °C for 15 minutes. After cooling to room temperature, the mixture was poured into 3 l of water, and extracted twice with ethyl acetate. The combined organic phases were washed with 5% Na_2CO_3, dried (Na_2SO_4) and concentrated *in vacuo*. High performance liquid chromatography (silica gel, eluting with 1:1 heptane:ethyl acetate) afforded 6.5 g of the product which was crystallized from heptane/acetone, m.p. 117-118 °C.

Analysis:			
Calculated for $C_{19}H_{22}N_2O_4$	66.65%C	6.48%H	8.18%N
Found:	66.56%C	6.64%H	8.12%N

EXAMPLE 2b

4-(N,N-DIETHYL)-7-MEHOXY-2-(4-PYRIDINYL)BENZOFURANAMIDE

The named compound was produced during the reaction leading to the formation of the N,N,-diethyl-4-methoxy-2-formyl-3-(4-pyridinylmethoxy)benzamide and was isolated in pure form in the chromatography step. Crystallization from heptane/acetone afforded 2.8 g of the named compound, m.p. 115-117 °C.

Analysis:			
Calculated for $C_{19}H_{20}N_2O_3$:	70.35%C	6.21%H	8.64%N
Found:	69.97%C	6.30%H	8.48%N

EXAMPLE 3

1-METHYL-4-(4-N,N-DIETHYLAMIDO-7-METHOXY-2-BENZOFURANYL)PIPERIDINIUM MALEATE

A mixture of 4-(N,N-diethyl)-7-methoxy-2-(4-pyridinyl)benzofuranamide(4.3 g), methyl iodide (2.55 g) and 2-butanone (30 ml) was stirred at 50 °C for 15 hours. The mixture was cooled to 0 °C, filtered and th resulting solid was washed with cold 2-butanone and heptan to give 4-[2-(4-diethylamido-7-methoxy-2-benzofuranyl)]-1-methyl pyridinium iodide. Th quaternary salt (6.0 g) was dissolved in methanol (100 ml) and a solution of $NaBH_4$ (5.0 g) in H_2O (20 ml) was added dropwise over 30 minutes. The mixture was stirred at ambient temperature for 16 hours, concentrated and the r sidual aqueous lay r was extracted with dichloromethane (hereinafter "DCM"). Th DCM extracts wer combined, washed with brine and con-

centrated to give N,N-diethyl-7-m thoxy-2-(1-m thyl-1,2,3-6-tetrahydro-4-pyridinyl)benzofuranamide.

T a solution of N,N-diethyl-7-methoxy-2-(1-methyl-1,2,3,6-t trahydro-4-pyridinyl)benzofuranamide (4.4 g) in methanol (120 ml) and 48% HBr (2.1 g) was added PtO_2 (160 mg) and the mixtur was hydrogenated in a Parr Shak r for 6 hours at room temperatur . Th mixtur was filt red and th m thanol was evaporated *in vacuo*. The residual solution was treated with 2N NH_4OH and extracted twice with DCM. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica gel, eluting with 5% MeOH/DCM containing 0.1% NH_4OH) afforded 2.1 g of product which was converted to the maleic acid salt in ethereal solution, m.p. 123-125 °C.

Analysis:			
Calculated for $C_{24}H_{32}N_2O_7$:	62.59%C	7.00%H	6.08%N
Found:	61.76%C	6.94%H	5.79%N

EXAMPLE 4

1-METHYL-4-(4-CYANO-7-METHOXY-2-BENZOFURANYL)PIPERIDINIUM MALEATE

To a solution of 1-methyl-4-(7-methoxy-2-benzofuranyl)piperidine (2.45 g) in anhydrous DCM under nitrogen was added chlorosulfonylisocyanate (2.2 g) dropwise via syringe at room temperature. The mixture was stirred at ambient temperature for 3 hours, then DMF (0.5 ml) was added, and the mixture was stirred for 15 hours. The reaction mixture was poured into water, and extracted twice with DCM. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica gel eluting with 5% MeOH/DCM containing 0.01% NH_4OH) afforded 1.55 g of product which was converted to the maleic acid salt in ethereal solution, m.p. 175-177 °C.

Analysis:			
Calculated for $C_{20}H_{22}N_2O_6$:	62.17%C	5.74%H	7.25%N
Found:	61.87%C	5.75%H	7.03%N

EXAMPLE 5

1-METHYL-4-(4-AMINOMETHYL-7-METHOXY-2-BENZOFURANYL)PIPERIDINE DIHYDROBROMIDE

To 1-methyl-4-(4-cyano-7-methoxy-2-benzofuranyl)piperidine (2.7 g) in anhydrous THF under nitrogen was added $LiAlH_4$ (30 ml of a 1 M solution in THF) dropwise at room temperature. The mixture was stirred at ambient temperature for 4 hours, and then water (2.0 ml) was added slowly under ice cooling. The precipitate was filtered and washed with ethyl acetate. The combined filtrates were dried (Na_2SO_4) and concentrated *in vacuo* to give 2.3 g of the crude product. Flash chromatography (silica gel, eluting with 20% MeOH/DCM + 0.1% NH_4OH) afforded the product, which was converted to the dihydrobromide salt in ethereal solution, m.p. 195 °C (dec.).

Analysis:			
Calculated for $C_{16}H_{24}Br_2NO_2$:	44.06%C	5.55%H	6.42%N
Found:	43.74%C	5.66%H	6.17%N

EXAMPLE 6

1-METHYL-4-(4-N,N-DIETHYLAMINOMETHYL-7-METHOXY-2-BENZOFURANYL)PIPERIDINE DIHYDROBROMIDE MONOHYDRATE

To N,N-diethyl-7-methoxy-2-(1-methyl-4-piperidinyl)benzofuranamide (2.1 g) in anhydrous THF (20 ml) at room temperature was added a 1 M $LiAlH_4$ solution in THF (6 ml) dropwise via syringe. The mixture was then heated to 50 °C for 3 hours and after cooling, water (0.5 ml) was carefully added. The mixture was filtered and the filter cake washed twice with ethyl acetate. The combined filtrates were dried (Na_2SO_4) and concentrated *in vacuo* to leave 1.7 g of an oil. To a solution of the oil in DCM was added an HBr solution in diethyl ether at room temperature. The resulting precipitate was filtered, washed with diethyl ether and crystallized from DCM, m.p. 226-229 °C (dec.).

Analysis:			
Calculated for $C_{20}H_{30}N_2O_2 \cdot 2HBr \cdot H_2O$:	47.07%C	6.72%H	5.49%N
Found:	46.78%C	6.67%H	5.33%N

EXAMPLE 7

2-(1-METHYL-4-PIPERIDINYL)-BENZOFURAN-7-YL METHYL CARBAMATE

A mixture of 1-methyl-4-(7-methoxy-2-benzofuranyl)piperidine (5.6 g) and 48% HBr (40 ml) was stirred at 120 °C for 30 minutes. After cooling to room temperature, the mixture was neutralized with 10% sodium hydroxide solution and extracted with 1:1 ethyl acetate/1-butanol. The organic extract was washed with brine, concentrated and the resulting oil was chromatographed (silica gel, eluting with 20% MeOH/DCM and 0.5% NH_4OH) to afford 1.9 g of 1-methyl-4-(7-hydroxy-2-benzofuranyl)piperidine.

To a mixture of 1-methyl-4-(7-hydroxy-2-benzofuranyl)piperidine (1.8 g) and a catalytic amount of CuCl in DMF (30 ml) was added methylisocyanate (0.7 ml) at room temperature under N_2. The mixture was then stirred for 16 hours at ambient temperature. Water and brine were added and the mixture was extracted with ethyl acetate. The organic phase was washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica gel, eluting with 10% MeOH/DCM + 0.2% NH_4OH) afforded the product, which was crystallized from ethyl acetate, m.p. 144-146 °C.

Analysis:			
Calculated for $C_{16}H_{20}N_2O_3$:	66.65%C	6.99%H	9.72%N
Found:	66.53%C	7.04%H	9.69%N

EXAMPLE 8

2-(4-PYRIDINYL)BENZOFURAN-7-YL METHYL CARBAMATE

A mixutre of 4-(7-methoxy-2-benzofuranyl)pyridine (5.0 g) and 48% HBr (50 ml) was stirred at 120 °C for 1 hour. The mixture was cooled to room temperature, neutralized with 10% NaOH and 5% Na_2CO_3 and extracted with ethyl acetate. The organic extract was washed with brine and concentrated to give 4-(7-hydroxy-2-benzofuranyl)pyridine.

To a mixture of 4-(7-hydroxy-2-benzofuranyl)pyridine (2.0 g) and a catalytic amount of CuCl in DCM (10 ml) and ethyl acetate (20 ml) was added methylisocyanate (1.0 ml) at room temperature under N_2. The mixture was stirred at ambient t mperature for 16 hours, diluted with methanol, filtered through Al_2O_3 and concentrated *in vacuo* to give 2.0 g of the crude product which was crystallized from ethyl acetate, m.p. 158-160 °C.

Analysis:			
Calculated for $C_{15}H_{12}N_2O_3$:	67.16%C	4.51%H	10.44%N
Found;	67.20%C	4.22%H	10.29%N

EXAMPLE 9

4-(7-METHOXY-2-BENZOFURANYL)-PYRIDINE

To a solution of o-vanillin (6.0 g) and 4-picolylchloride hydrochloride (6.6 g) in DMF (70 ml) was added potassium carbonate (20.0 g) and potassium iodide (2.0 g). The mixture was stirred vigorously for 8 hours at 150 °C. The mixture was filtered hot and the filter cake was washed with ethyl acetate. The organic phases were combined and concentrated *in vacuo* to a volume of about 10 ml, poured into water and extracted twice with ethyl acetate. The combined organic layers were washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica gel, eluting with 1:2 heptane:ethyl acetate) afforded 2.5 g of the product, which was crystallized from heptane/ethyl acetate, m.p. 140-141 °C.

Analysis:			
Calculated for $C_{14}H_{11}NO_2$:	74.65%C	4.92%H	6.22%N
Found:	74.67%C	4.73%H	6.09%N

EXAMPLE 10

2-(4-PYRIDINYL)BENZOFURAN-7-YL BUTYL CARBAMATE

To a mixture of 4-(7-hydroxy-2-benzofuranyl)pyridine (1.1 g) and 1,8-diazabicyclo[5.4.0]undec-7-ene (150.0 mg) in acetonitrile (20 ml) was added n-butylisocyanate (0.5 g) at room temperature under N_2. The mixture was then stirred at ambient temperature for 3 hours. The crude product which precipitated out of the reaction mixture was filtered and crystallized from ethyl acetate, then chromatographed silica gel, 2:1 heptane/acetone) to remove residual impurities. Concentration of the appropriate fractions afforded the product, m.p. 140 °C.

Analysis:			
Calculated for $C_{18}H_{18}N_2O_3$:	69.66%C	5.85%H	9.03%N
Found:	69.27%C	5.42%H	8.96%N

EXAMPLE 11

1-METHYL-4-(7-METHOXY-2-BENZOFURANYL)PIPERIDINE

A mixture of 4-(7-methoxy-2-benzofuranyl)pyridine (66 g), methyl iodide (56.7 g) and 2-butanone (800 ml) was stirred at 50 °C for 4 hours, cooled to room temperature, filtered and the resulting solid was washed with 2-butanone to provide 1-methyl-4-(7-methoxy-2-benzofuranyl)pyridinium iodide, m.p. 225-227 °(dec.). The quaternary salt (90 g) was dissolved in methanol (1 l) and a solution of $NaBH_4$ (40 g) in H_2O (250 ml) was added dropwise. The mixture was stirred at ambient temperature for 3 hours, concentrated and the residual aqueous layer was extracted with DCM. The extracts were combined, washed with brine and concentrated to give 1 methyl-4-(7-methoxy-2-benzofuranyl)-1,2,3,6-tetrahydropyridine.

A mixtur of 1-methyl-4-(7-methoxy-2-benzofuranyl)-1,2,3,6-tetrahydropyridine (58.0 g), methanol (1.5 l), water (200 ml), 48% HBr (42.0 g), and platinum dioxide were shaken under hydrogen at room temperature for 6 hours. The mixture was filtered; the filtrate was concentrated *in vacuo* to the aqueous phase, neutralized with 5% Na_2CO_3 and xtracted with CH_2Cl_2. Th organic phase was washed with water, dried (Na_2SO_4) and concentrated *in vacuo* to give 59 g of th crude product, which was crystallized from

m thanol/water, m.p. 74-75 • C.

Analysis:			
Calculated for $C_{15}H_{17}NO_2$:	73.44%C	7.81%H	5.71%N
Found:	73.47%C	7.83%H	5.65%N

EXAMPLE 12

2-(4-PIPERIDINYL)BENZOFURAN-7-YL DIMETHYL CARBAMATE HEMIFUMARATE

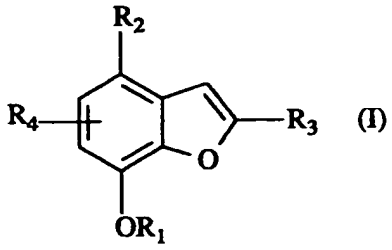
To a mixture of 1-methyl-4-(7-hydroxy-2-benzofuranyl)piperdine (3.8 g), triethylamine (1.2 g), DBU (0.3 g) in acetonitrile (20 ml) was added a solution of dimethyl cabamoyl chloride (1.4 g) in acetonitrile (10 ml). The mixture was stirred at ambient temperature overnight, concentrated and chromatographed (silica gel eluting with 10% MeOH/DCM) to afford 1.2 g of 2-(1-methyl-piperdin-7-yl)benzofuran-7-yl dimethyl carbamate after recrystalization from ethanol.

To a suspension of 2-(1-methyl-piperdin-7-yl)benzofuran-7-yl dimethyl carbamate (1.0 g) in dichloroethane (10 ml) was added chloroethyl chloroformate (0.47 g) and the mixture was refluxed for 3 hours. After stirring at room temperature overnight, an additional 0.95 gram of 2-chloroethyl chloroformate was added and the mixture refluxed for 6 hours. The mixture was concentrated, 10 ml of methanol was added and the mixture was heated to reflux for 2 hours. After concentration, the residue was chromatographed (silica gel, 10% MeOH/CH_2CH_2 containing 0.5% NH_4OH) and the fractions were evaporated. The product was dissolved in ethyl acetate and a solution of fumaric acid in ether was added; the resulting solid was collected and dried, m.p. 195-196 • C.

Analysis:			
Calculated for: $C_{18}H_{22}N_2O_5$	62.42%C	6.40%H	8.09%N
Found:	62.25%C	6.38%H	7.98%N

Claims

1. A compound of the formula I



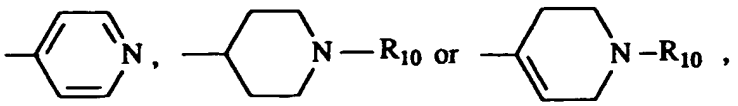
(I)

wherein

R_1 is hydrogen, loweralkyl, aryllowerlalkyl, $CONHR_{11}$ or $CONR_6R_7$

R_2 is hydrogen, cyano, $CH_2NR_8R_9$, $CONHR_5$ or $CONR_6R_7$;

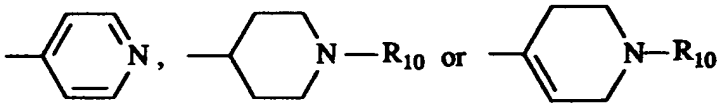
R_3 is



where R_{10} is hydrogen, loweralkyl, aryllowerlalkyl, $CONHR_5$, $CONR_6R_7$, acyl, acyloxyloweralkyl or

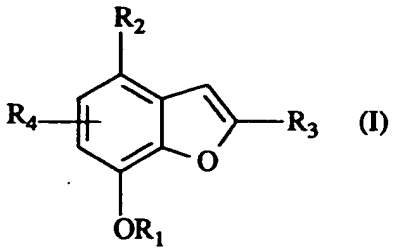
acyloxyarylIow ralkyl;
R_4 is hydrogen, halog n, loweralkyl or loweralkoxy;
R_5 is hydrogen, loweralkyl or aryIloweralkyl;
R_6 is low ralkyl or aryllow ralkyl;
R_7 is loweralkyl or aryIloweralkyl;
R_8 is hydrogen, loweralkyl, aryIloweralkyl or acyl;
R_9 is hydrogen, loweralkyl or aryIloweralkyl;
R_{11} is loweralkyl, aryl or aryIloweralkyl;
with the proviso that if R_1 is hydrogen or loweralkyl, R_2 cannot be hydrogen;
or a pharmaceutically acceptable acid addition salt thereof, or, where applicable, an optical or geometric isomer or racemic mixture thereof.

2. A compound of formula I as defined in claim 1,
where
R_1 is $CONHR_{11}$ or $CONR_6R_7$;
R_2 is $CH_2NR_8R_9$, $CONHR_5$ or $CONR_6R_7$;
R_3 is



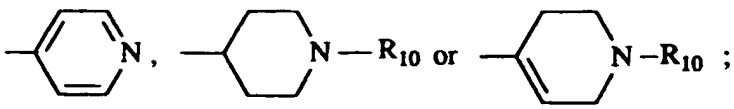
where R_{10} is hydrogen or loweralkyl;
R_4 is hydrogen or halogen;
R_5 is hydrogen or loweralkyl;
R_6 is loweralkyl;
R_7 is loweralkyl;
R_8 is hydrogen or loweralkyl;
R_9 is hydrogen or loweralkyl; and
R_{11} is loweralkyl, aryl or aryIloweralkyl.

3. A compound of the formula I



(I)

wherein
R_1 is loweralkyl;
R_2 is cyano, $CH_2NR_8R_9$ or $CONR_6R_7$;
R_3 is



;

R_4 is hydrogen;
R_5 is loweralkyl;

R_6,R_7,R_8,R_9 and R_{10} ar loweralkyl.

4. A pharmaceutical composition which comprises an effective amount of a compound as defined in claim 1 and a pharmaceutically acceptabl carri r therefor.

5. The use of a compound as claimed in claims 1 or 2 as a pharmaceutical.

6. The use of a compound as claimed in claim 1 or 2 for the production of a pharmaceutical having an activity as anticholinesterase inhibitor.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 11 1962

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	EP-A-0 338 782 (MERCK FROSST CANADA INC.) 25 October 1989 * claim 1 *	1,4,5	C07D405/04 C07D307/86 A61K31/44 A61K31/445
X	EP-A-0 165 810 (MERCK FROSST CANADA INC.) 27 December 1985 * claim 1 *	1,4,5	
X	US-A-4 210 655 (SCHENKER ET AL.) 1 July 1980 * claims 1-4 *	1,5	
A	* see examples 3,14,21 and 27 *	1	
Y	EP-A-0 468 187 (EISAI CO., LTD.) 29 January 1992 * see examples 49, 59 and 65 * * page 15 - page 17; claims 1-6,10,11 *	1-6	
Y	EP-A-0 296 560 (EISAI CO., LTD.) 28 December 1988 * see example 28 * * page 31 - page 33; claims 1-9,12-15 *	1-6	TECHNICAL FIELDS SEARCHED (Int.Cl.6) C07D A61K
Y	EP-A-0 259 621 (A/S FERROSAN) 16 March 1988 * see examples 6,7,8,16d,28,29,39 and 40 * * claims 1,4 *	1-6	
A	EP-A-0 542 671 (CIBA-GEIGY AG) 19 May 1993 * see formulae VIIa, VIIb and VIIc, page 7 and formula XII, page 10 * * claims 18,29,30 *	1-5	
A	EP-A-0 398 413 (DUPHAR INTERNATIONAL RESEARCH B.V.) 22 November 1990 * see compounds 1,2,10,12,14,37,40,42 and 43 * * claim 1 *	1-5	

-/--

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	19 September 1994	Hartrampf, G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EUROPEAN SEARCH REPORT

Application Number
EP 94 11 1962

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	EP-A-0 217 530 (ELI LILLY AND COMPANY) 8 April 1987 * claim 1 * ---	1-5	
A	EP-A-0 006 524 (CIBA-GEIGY AG) 9 January 1980 * the whole document * -----	1-5	
			TECHNICAL FIELDS SEARCHED (Int.Cl.6)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	19 September 1994	Hartrampf, G

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X : particularly relevant if taken alone
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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